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- (54) **Pharmacologically active 2-and 3-substituted (1', 5'-diaryl-3-pyrazolyl)-N-Hydroxypropanamides and method for synthesizing.**

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| EP-A- 0 014 508 | EP-A- 0 014 847 |
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| EP-A- 0 248 594 | DE-A- 2 633 992 |
| DE-A- 3 630 553 | DE-B- 1 946 370 |
| FR-A- 2 574 399 | US-A- 4 694 018 |

ARZNEIMITTEL-FORSCHUNG (DRUG RE-SEARCH) vol.24, no. 4, 1974, pages 494-499, Aulendorf, DE; U.JAHN et al.

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INDIAN JOURNAL OF CHEMISTRY, vol. 17B,
May 1979, pages 472-477, Lucknow; V. VIR-
MANI et al.

JOURNAL OF ORGANIC CHEMISTRY vol. 44,
no. 13, 1979, pages 2073-2077, Easton, PA,
US; M.R.DETTY.

Description

The present invention relates to 2- and 3-substituted pyrazole propionic acid derivatives, and particularly to N-hydroxy, N-alkyl pyrazole propanamide analogs of these compounds which are pharmacologically active in alleviating inflammation, asthma, hypersensitivity, myocardial ischemia, dermatological conditions such as psoriasis, dermatitis and gastrointestinal inflammatory conditions such as inflammatory bowel syndromes, and to a method for synthesizing those pyrazole derivatives.

Nonsteroidal anti-inflammatory drugs (NSAID's) such as indomethacin, naproxen, ibuprofen, tolectin, fenoprofen and the like have generally been shown to attenuate the biosynthesis of prostaglandins by inhibiting the activity of the enzyme cyclooxygenase. The prostaglandin end-products of the cyclooxygenase pathway are responsible for many of the early signs of inflammation including hyperalgesia, increases in vascular permeability leading to edema, and pyrexia. The activity and potency of the NSAID's in reducing these signs and symptoms is, for the most part, correlated with their ability to inhibit prostaglandin biosynthesis.

The other major pathway of arachidonic acid metabolism is the lipoxygenase pathway. Lipoxygenase products of arachidonate metabolism, the leukotrienes, hydroxyeicosatetraenoic acids (HETES) and hydroperoxyeicosatetraenoic acids (HPETES), have been shown or implicated to be involved in disease states including acute and chronic inflammation, arthritis, allergic and other hypersensitivity disorders, dermatological diseases such as psoriasis, acne, atopic dermatitis, contact sensitivity, eczema and others, cardiovascular disorders secondary to myocardial ischemia or infarction, thromboembolism or vasculitis or platelet aggregation, and hyperalgesic disorders, gynecological disorders such as dysmenorrhea, ocular inflammation, sperm motility or function, and others.

Leukotriene B₄ (LTB₄), another product of the lipoxygenase pathway, as well as HETES and HPETES can mediate induction of other phlogistic substances such as thromboxanes and prostacyclin, is chemotactic to inflammatory cells, and is hyperalgesic. Many of these mediators have been identified in skin, lungs, coronary circulation, eyes, gastrointestinal tract and other organs, and in the synovial fluid of rheumatoid arthritic patients. In chronic inflammatory conditions such as rheumatoid arthritis, it is believed to be the chronic influx of leukocytes, probably mediated by LTB₄, that is the eventual cause of joint erosion.

It is believed that inhibitors of the lipoxygenase pathway could lead to a relatively permanent effect on inflammatory disorders such as rheumatoid arthritis since they could modulate the actual mechanisms of tissue and joint breakdown. Similarly, drugs that could inhibit prostaglandin synthesis via the cyclooxygenase pathway could modulate and reduce early manifestations of inflammation. Pharmacologically active compounds that can inhibit both enzyme pathways at similar concentrations (dual inhibitors) provide a more complete relief for patients suffering from arthritis, hypersensitivity, dermatological, cardiovascular, gastrointestinal, ocular, and gynecological disorders than present drugs that inhibit one pathway, but not the other as is the case for usually used NSAID's that are predominantly inhibitors of the cyclooxygenase (prostaglandin synthesis) pathway.

A number of 1,5-diaryl-3-substituted pyrazoles are reported in the literature. Some of those pyrazoles have been reported to have pharmacological activity.

For example Fulmer et al., *J. Het. Chem.*, 17:799-800 (1980) report the synthesis of 1,3,5-triaryl pyrazoles, as do Foote et al., *J. Het. Chem.*, 7:89-92 (1970), Beam et al., *J. Het. Chem.*, 9:183-185 (1972); Soliman et al., *J. Pharm. Sci.*, 70:606-610 (1981), and Barluenga et al., *J.C.S. Chem. Comm.*, 891 (1979). Soliman et al., *J. Pharm. Sci.*, 70:602-605 (1981) also report synthesis of 3-methyl-1,5-diarylpyrazoles in which the 1-position aryl is a phenylsulfonylurea or thiourea. Of the above reports, only the two reports by Soliman et al. discuss any pharmacological activity for the pyrazoles prepared or for analogs of those pyrazoles, and those materials are reported to have hypoglycemic activity.

Virmani et al., *Indian J. Chem., Sect. B*, 17B: 472-477 (1979) report the synthesis of 3-omega-alkylaminoalkyl pyrazoles among other compounds. The 1,5-diaryl-3-substituted pyrazoles reported contained a phenyl group at the 1-position, a 4-nitrophenyl at the 5-position, and a (CH₂)_n-NHCH₃ group at the 3-position, where n is 3,4 or 5 (3-5). This report stated that the compounds prepared were screened for a number of biological activities, with nine of the ninety-four numbered compounds synthesized having mild anti-inflammatory activity, two others having diuretic activity and two others having weak anti-cancer activity. The above-discussed 1,5-diaryl-3-substituted pyrazoles were not among the compounds reported to have any pharmacological activity.

Vereshchagin et al., *Zh. Org. Khim.*, 7:907-912 (1971) reported the synthesis of 1,5-diaryl-3-substituted pyrazoles. The 3-substituents were reported to be alkoxy alkylene in which the alkoxy radical was methoxy or phenoxy and the alkylene was methylene or isopropylene, while the 1,5-diaryl radicals were unsubstituted phenyl.

Jahn and Wagner-Jauregg, *Arzneim-Forsch. (Drug Res.)*, 24:494-499 (1974) reported the synthesis and some pharmacological activities of 1,5-diaryl-3-substituted-4,5-dihydropyrazoles. The aryl group at the 1-position for each reported compound was phenyl, while the 5-aryl substituent was reported to be phenyl, 4-methoxyphenyl, 3-methoxy-4-hydroxyphenyl, and 2-hydroxyphenyl. The before-mentioned pyrazoles were substituted at the 3-position by bonding to the 3-position of propionic acid or propiohydroxamic acid. These compounds were said to possess antirheumatic activity.

Shawali et al., *J. Het. Chem.*, 13:989-92 (1976); Shawali, *J. Het. Chem.*, 14:375-81 (1977); and Matsumoto et al., *Bull. Chem. Soc. Japan*, 47: 946-949 (1979) reported the synthesis of 1,5-diaryl-3-substituted pyrazoles, all of which also included a substituent other than hydrogen at the 4-position on the pyrazole ring. Exemplary 4-position substituents were reported to include cyano, amino, carboethoxy, and phenylcarbonyl. These reports included no mention of biological activity of the compounds reported.

A series of benzimidoylpyrazoles was reported by Shrof et al., *J. Med. Chem.*, 24:1521-1525 (1981). These compounds were reported to possess activities of sulfonyl urea and biguanide hypoglycemics.

Biere et al., *Arch. Phar.*, 316:608-616 (1983) reported the synthesis of 1,4-diaryl-pyrazole-3-acetic acid derivatives, some of which also contained an aryl substituent at the 5-position. The synthesized compounds were assayed for use as anti-inflammatory drugs in rats. The compounds assayed that also contained 5-position substituents were reported to be relatively inactive.

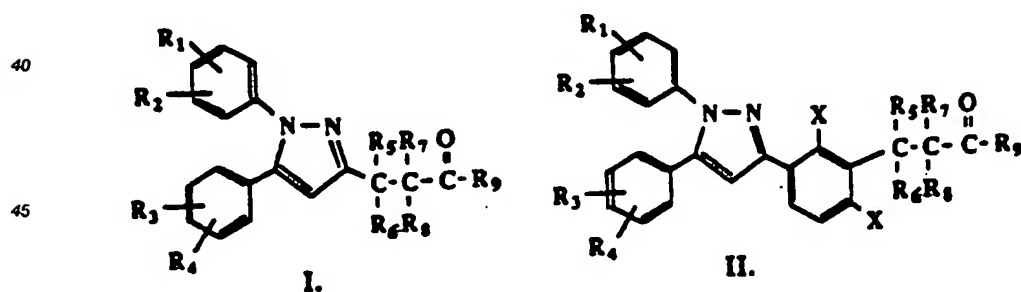
A further group of 1,5-diphenyl-4-substituted-pyrazole-3-acetic acids was reported by El-Sayed and Ohta, *Bull. Chem. Soc. Japan*, 46:1801-1803 (1973). Those compounds were utilized as intermediates in the synthesis of pyrazolo-[4,3-c]-pyridines. Another group of 1,5-diphenyl-4-substituted-pyrazoles, some of which also include methyl, phenyl and carboxymethyl groups at the 3-position, was reported in Al-Saleh et al., *J.C.S. Perkin I*, 642-645 (1981). The reports of El-Sayed and Ohta and those of Al-Saleh et al. make no mention of the pharmacological properties of the pyrazole derivatives reported. Another group of 1,5-diaryl-3,4-disubstituted pyrazoles and 4,5-dihydro-5-hydroxy pyrazoles was reported in Fusco and Croce, *Gazz. Chim. Ital.*, 101:703-272 (1971).

Summary of the Invention

In EP-A-O 284 594, a series of 1,5-substituted pyrazoles is described in which the side chain on the pyrazole ring is unsubstituted.

The present invention relates to 2- and 3-substituted (1',5'-diaryl-3'-pyrazolyl)-propionic acid derivatives, their use and methods of synthesis. The compounds of the present invention are pharmacologically active in alleviating inflammation, and inhibit the cyclooxygenase enzyme pathway, the lipooxygenase enzyme pathway, or preferably both pathways.

In particular, the invention contemplates a substituted pyrazole compound having a structure that conforms to formula I or II.



wherein, in Formula I:

(A) R_1 , R_2 , R_3 and R_4 are the same or different and are hydrogen, lower alkyl, lower alkoxy, amino, acetamido, phenyl, halo, hydroxy, lower alkylsulfonyl, lower alkylthio, nitro, trifluoromethyl, ω -trifluoromethyl lower alkoxy; or

R_1 and R_2 , or R_3 and R_4 , taken together with the phenyl group to which they are attached, form a naphthyl or substituted naphthyl group;

(B) R_9 is hydroxy, $-OR_{10}$ or $-N(OH)R_{10}$ wherein R_{10} is lower alkyl; and

(C) R_5 , R_6 , R_7 and R_8 are the same or different and are: hydrogen or lower alkyl; or

R_5 and R_6 , or R_7 and R_8 , when taken together are part of a spirocycloalkyl ring having 5-7 carbon

atoms; or R_5 , R_6 , R_7 and R_8 when taken together are part of an aryl or a heterocyclic ring; or R_6 and R_8 when taken together are part of a cyclohexyl, cyclohexenyl or 7-oxobicyclo[2.2.1]heptenyl ring; or R_5 , R_6 and R_7 are hydrogen and R_8 is phenyl, substituted phenyl (wherein the substituent is lower alkoxy, di lower alkoxy, carboxymethyl or carboxy), biphenyl, naphthyl or 4-chlorophenyl, provided that when R_8 is 4-chlorophenyl R_1 is 4-methoxy, R_2 is H, R_3 is 4-chloro, R_4 is H and R_9 is hydroxy, ethoxy or $N(OH)CH_3$; or R_5 , R_7 are R_8 are hydrogen and R_6 is phenyl, substituted phenyl (wherein the substituent is halo, lower alkyl or lower alkoxy), biphenyl, naphthyl or heterocycloaryl, provided that at least one of R_5 , R_6 , R_7 and R_8 is other than H, and the pharmaceutically acceptable salts thereof.

In Formula II: R_1 , R_2 , R_3 and R_4 are as defined in Formula I; X is lower alkoxy; R_5 , R_6 , R_7 and R_8 are hydrogen and R_9 is selected from hydroxy, lower alkoxy and $N(OH)CH_3$.

In preferred practice, R_1 and R_2 are lower alkoxy having 1-4 carbon atoms or hydrogen, and R_3 and R_4 are selected from the group consisting of halo, trifluoromethyl, lower alkyl and lower alkoxy.

The present invention also contemplates a pharmaceutical composition that comprises an anti-inflammatory amount of an above-described N-hydroxypropanamide compound dispersed in a pharmaceutically acceptable carrier. The dose may be administered by topical, p.o., parenteral or aerosol routes. In preferred practice, the substituted N-hydroxypropanamide compound is capable of inhibiting both the cyclooxygenase and the lipoxygenase pathways in the amount present in the composition, when the composition is introduced into a mammal.

Further contemplated is their use as anti-inflammatory agents by means of a pharmaceutical composition that includes as the active ingredient an effective amount of an above-described N-hydroxypropanamide compound dispersed in a pharmaceutically acceptable carrier for topical, oral, parenteral and aerosol administration.

A method for synthesizing a 1',5'-diaryl-3-pyrazolyl-N-hydroxypropanamide is also contemplated.

The present invention provides several benefits and advantages.

A particular benefit of the invention is that it provides pharmacologically active compounds that are useful in treating inflammatory conditions.

Another benefit of the present invention is that some of its pharmacologically active compounds inhibit the cyclooxygenase enzyme pathway, thereby providing a further means for studying that biological process.

Another advantage of the present invention is that some of its pharmacologically active compounds inhibit the lipoxygenase enzyme pathway, thereby providing a further means for studying that biological process.

Still further benefits and advantages of the present invention will be apparent to those skilled in the art from the detailed description and Examples that follow.

Detailed Description of the Invention

1',5'-Diaryl-3-pyrazolyl-N-hydroxypropanamide compounds, pharmaceutical compositions containing a substituted propanamide compound as an active ingredient, their use as anti-inflammatory agents and a method of synthesizing the substituted propanamide compound are contemplated herein.

In the above formula, R_1 , R_2 , R_3 and R_4 are substituents on phenyl rings that substitute for hydrogen atoms at positions 1 and 5 of the pyrazole ring. It is preferred that at least one of R_1 and R_2 , and one of R_3 and R_4 be substituted at the 4-positions of their respective phenyl rings.

In examining the above structural formula to which the useful N-hydroxypropanamide compounds conform, it is noted that the R_1 , R_2 , R_3 and R_4 radicals can be a "lower" alkyl, "lower" alkoxy. Groups and radicals referred to as "lower" denote that they possess 1 to 6 carbon atoms. The same is true for "lower" groups and radicals that are substituents of the "lower" groups and radicals enumerated.

Lower alkyl radicals include, for example, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, 2-methyl-3-butyl, 1-methylbutyl, 2-methylbutyl, neopentyl, *n*-hexyl, 1-methylpentyl, 3-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 2-hexyl, 3-hexyl, and the like.

Lower alkoxy radicals are oxygen ethers formed from a before-described lower alkyl group. Exemplary radicals include methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, and the like.

Lower alkylthio radicals of R_1 , R_2 , R_3 and R_4 are sulfide ethers and are thus analogous to the oxygen ethers described above.

Halo radicals preferably include chloro and bromo, as well as fluoro and iodo.

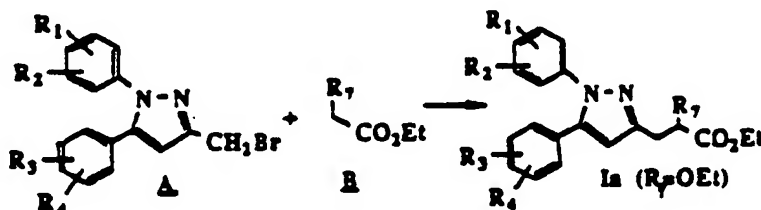
Lower alkylsulfonyl radicals contain a before-described lower alkyl radical bonded to an SO₂ moiety that is itself also bonded to a phenyl ring. Exemplary lower alkylsulfonyl radicals thus include methylsulfonyl, ethylsulfonyl, 2-ethylbutylsulfonyl and the like.

An omega-trifluoromethyl lower alkoxy radical is a lower alkoxy radical as before described that additionally includes a trifluoromethyl group at a position farthest on the alkyl chain from the place of bonding to the phenyl ring. Exemplary of such radicals are the 2,2,2-trifluoromethylethoxy.

Naphthyl and substituted naphthyl radicals can replace an aryl group herein at either the 1- or 2-positions to provide 1-naphthyl or 2-naphthyl substituents, respectfully. Substituents on the naphthyl radicals can be any of those described herein as being useful aryl substituents. Exemplary substituted 1- and 2-naphthyls include 6-methoxy-2-naphthyl and the like.

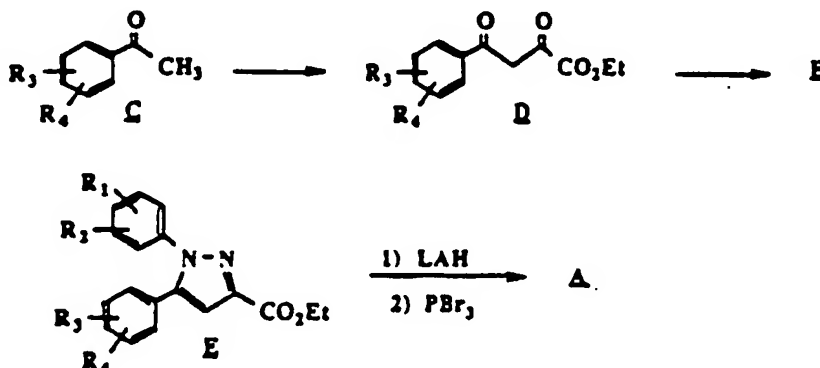
The compounds of structure I in which R₉ is O-lower alkyl are synthesized by addition of the appropriately substituted 3-bromomethyl-1,5-diphenylpyrazole A to the anion of the appropriately substituted aryl ester B generated by treatment with sodium hydride in a suitable solvent such as dimethylformamide according to Scheme 1 (R₇ = Aryl).

SCHEME 1



The 3-bromomethylpyrazole A is synthesized as depicted in Scheme 2. The 4-aryl-2,4-dioxobutanoate D is synthesized by treatment of the anion of acetophenone C with a dialkyl oxalate such as diethyl oxalate and then converted to the 3-carboalkoxypyrazole E with the appropriately substituted phenylhydrazine. Reduction with LiAlH₄ gave the corresponding hydroxymethyl analog which was then converted to the bromomethylpyrazole A with Phosphorus tribromide.

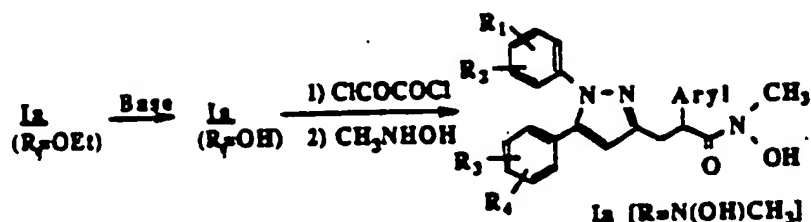
SCHEME 2



The compounds of Structure I in which R₉ is hydroxy and N(OH)Me are synthesized as shown in Scheme 3. Hydrolysis of the ester with aqueous base such as sodium or potassium hydroxide gives the pyrazole propionic acid (R₉ = OH) which upon treatment with oxalyl chloride in a suitable solvent such as CH₂Cl₂, for example, affords the corresponding acyl chloride which is then converted with an N-

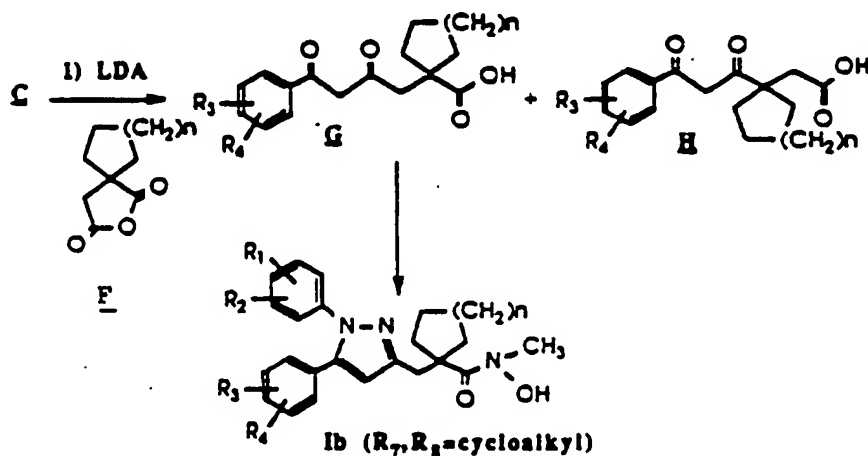
alkylhydroxylamine such as N-methylhydroxylamine to the hydroxamic acid ($R_9 = N(OH)R_{10}$ where R_{10} is lower alkyl).

SCHEME 3



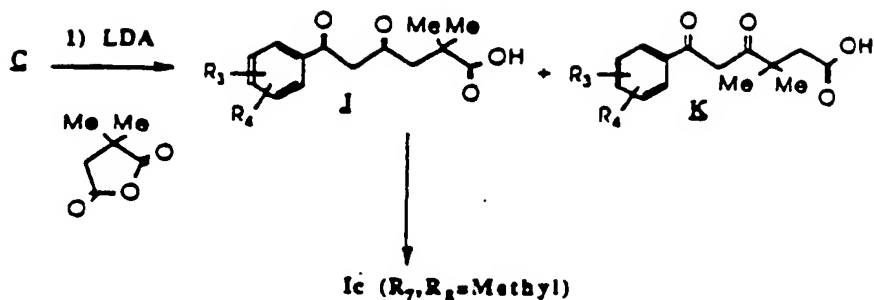
The compounds of Structure Ib in which R_5 , R_6 or R_7 , R_8 is a spiroalkyl group are synthesized by the route shown in Scheme 4. Treatment of the anion of the appropriately substituted acetophenone **C** with a cycloalkyl-1-carboxy-1-acetic acid anhydride **F** ($n=1-3$) affords a mixture of 2- and 3-spiroalkyl diketoheptanoic acids **G** and **H** from which the major isomer **G** is isolated by chromatography or recrystallization. Treatment of **G** with the appropriately substituted phenylhydrazine gives the 2-cycloalkylsubstituted pyrazole propionic acid which is then converted to hydroxamic acid Ib by the standard procedure and separated from the corresponding 1,3-diphenyl pyrazole isomer by chromatography and recrystallation.

SCHEME 4



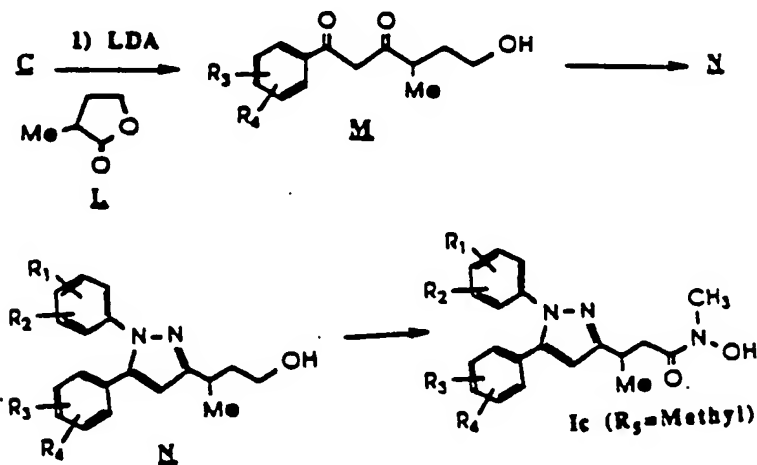
The compounds of Structure Ic in which R_5 , R_6 or R_7 , R_8 are each lower alkyl such as dimethyl are synthesized from diketo acids **J** and **K** in a similar manner to the spirocycloalkyl analogs above as shown in Scheme 5 for the dimethyl case.

SCHEME 5



20 Those compounds of structure Ic in which either R_5 or R_7 is lower alkyl were synthesized by treatment of the anion of ketone **C** with the appropriately substituted butyrolactone **L** to give the corresponding 1-aryl-1,3-dioxohexanol **M** which is condensed with the appropriate phenylhydrazine to afford pyrazole alcohol **N** and its 1,3-isomer. The isomers can be separated by chromatography. Oxidation with a suitable oxidizing agent such as, for example, Jones reagent to the propionic acid followed by hydroxamic acid formation by the above described procedure gives Ic. Scheme 6 illustrates this process when R_5 is methyl.

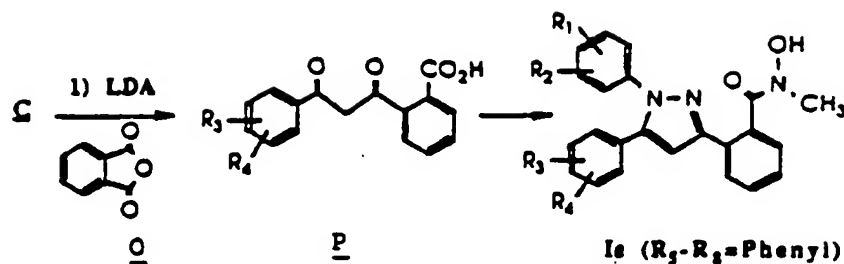
SCHEME 6



50 Alternatively, the compounds of Structure Ic in which either R_5 or R_7 is lower alkyl such as methyl, for example, may be synthesized by the method shown in Scheme 5 by treatment of the anion of ketone **C** with 4-methylsuccinic anhydride, separation of the isomeric diketo acids by chromatography and subsequent conversion to the pyrazole derivatives.

55 The compounds having an aryl, cycloalkyl or heterocyclic ring in the side chain are synthesized by treatment of the anion of acetophenone **C** with the appropriate bicyclic anhydride **O** to afford diketo acid **P** which is then transformed to the hydroxamic acid by the methods described above. Scheme 7 depicts the synthesis of these compounds when the bicyclic anhydride is phthalic anhydride.

SCHEME 7



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The compounds of Structure Ia' in which R₅ is O-lower alkyl are synthesized as shown in Scheme 8. The hydroxymethyl pyrazole derivative, synthesized as described in Scheme 2 from compound E, is oxidized to aldehyde U with a suitable oxidizing agent such as, for example, CrO₃ in pyridine. Treatment of the aldehyde with the appropriately substituted Grignard reagent V affords the alcohol W which is then oxidized with a suitable oxidizing agent such as, for example, pyridinium chlorochromate to the ketone X. A modified Wittig reaction of the ketone X with triethyl phosphonoacetate gives the ethyl pyrazole cinnamates Y as a mixture of E and Z isomers which can be separated by chromatography or reduced directly by catalytic hydrogenation with Pd/C to the propanoate Ia'. The esters can also be prepared from the corresponding pyrazole propionic acids by esterification with an esterifying agent such as diazomethane, for example.

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The compounds of Structure Ia' in which R₅ is hydroxy and N(OH)Me are synthesized using the identical steps shown in Scheme 3 for the corresponding derivatives of Structure Ia.

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Additional aryl derivatives were synthesized by treatment of aldehyde U with an arylmagnesium halide or with an aryl halide or activated aryl derivative such as 2-methoxybenzene and butyllithium at -78°C to give alcohol W'. Subsequent conversion to Y' was carried out as described in Scheme 8. Compounds of Structure Y' were converted to the unsaturated acids A' and subsequently to the hydroxamic acids B' following the procedures described for the 2-aryl derivatives shown in Scheme 2. The overall scheme for the conversion of U to B' is depicted in Scheme 8'. Aryl derivatives synthesized include phenyl, substituted phenyl, biphenyl, naphthyl, substituted naphthyl, and heterocyclic aryl such as thienyl and furyl.

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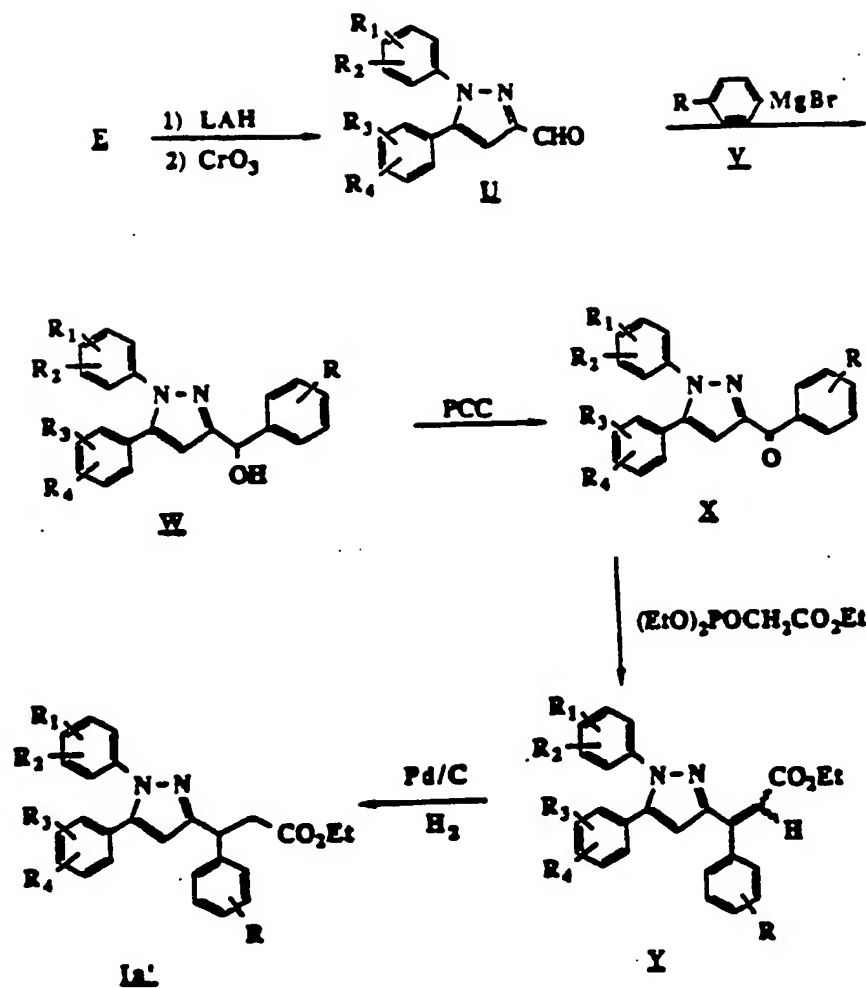
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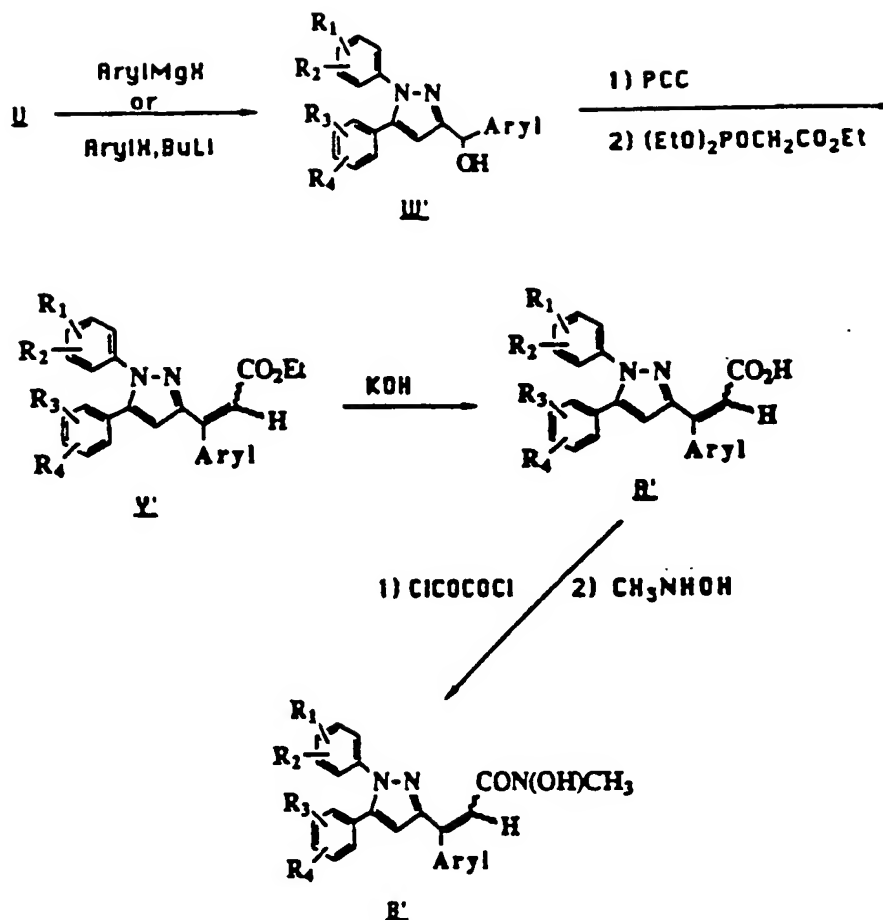
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SCHEME 8



SCHEME 8'



The compounds of structure **II** are synthesized by the route shown in Scheme 9. Alkylation of dihydroxyacetophenone **Q** with an alkylating agent such as methyl iodide, for example, with a base such as potassium carbonate in a suitable solvent such as acetone gives the corresponding 2,4-dialkoxy analog which upon treatment with the appropriate phenylhydrazine affords the hydrazone **R**. Formation of the dianion of **R** with a base such as butyl lithium followed by treatment with the appropriately substituted benzoate ester such as methyl 4-chlorobenzoate gives pyrazole **S**. Hydroboration of the terminal double bond with borane-methyl sulfide complex afforded the primary alcohol **T** which was transformed to hydroxamic acid **II** by the procedures described in Scheme 6.

SCHEME 9

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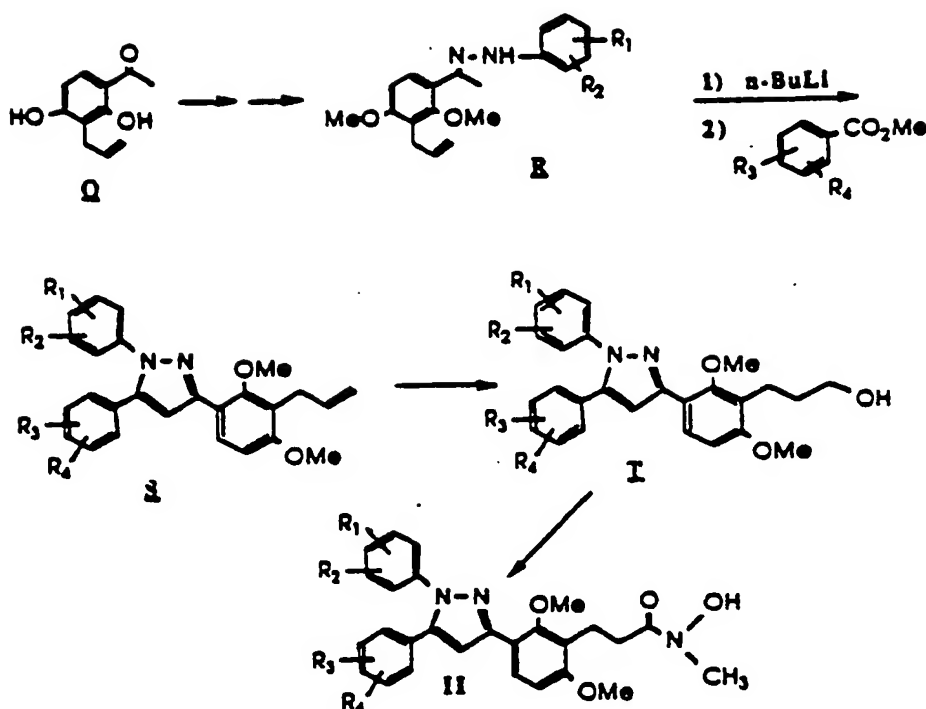
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The intermediates used in the preparation of the N-hydroxypropanamides are also novel compounds and are included as part of the present invention. Basic salts of those carboxylic and hydroxamic acids are also contemplated, and are formed by treatment of the acid with an appropriate, non-toxic, pharmaceutically acceptable alkaline reagent to form a carboxylate or hydroxamate cation salt. Exemplary non-toxic, pharmaceutically acceptable cation salts of such carboxylic and hydroxamic acids include sodium, potassium, zinc, aluminum, calcium and magnesium. These salts also readily form in aqueous solutions of the carboxylic and hydroxamic acids.

Specific, particularly preferred compounds of this invention are named hereinbelow, followed by a parenthesized, underlined numeral for ease of identification and correlation with the syntheses and anti-inflammation study described in detail hereinafter.

The preferred species of this invention include:

1. Ethyl 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-phenylpropanoate (8);
2. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-(4-chlorophenyl)-N-hydroxy-N-methylpropanamide (26);
3. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-2-spirocycloheptyl-N-methylpropanamide (42);
4. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2,N-dimethyl-N-hydroxypropanamide (52);
5. 2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)pyrazolyl-3-yl]-N-hydroxy-N-methylbenzamide hemihydrate (62);
6. cis-2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-1-(N-hydroxy-N-methyl)carboxamidocyclohexane (63);
7. 3-[3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)pyrazol-3-yl]-2,6-dimethoxyphenyl]-N-hydroxy-N-methylpropanamide (75).
8. [1,5-Bis(4-methoxyphenyl)-3-pyrazolyl]-1-phenylmethanol (105).
9. 1-(4-Methoxyphenyl)-3-(4-methylbenzoyl)-5-(4-methylphenyl)pyrazole (109).
10. (Z)-Ethyl 3-[1(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-(4-methylphenyl)propenoate (125).

11. 3-(4-Fluorophenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl] propanoic acid (151).
12. (E)-3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenyl-2- propenoic acid (155).
13. (E)-3-(4-Chlorophenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3- pyrazolyl]propanoic acid (157).
14. (Z)-3-(4-Chlorophenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3- pyrazolyl]propanoic acid (158).
15. (E)-3-(4-Fluorophenyl)-N-hydroxy-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-N-methyl-
propanamide (163).

A pharmaceutical composition that comprises an anti-inflammatory amount of a compound of this invention dispersed in a pharmaceutically acceptable carrier is also contemplated herein. The composition comprises a unit dosage of the substituted pyrazole compound.

The substituted N-hydroxypropanamide compounds of this invention are capable of inhibiting the lipoxygenase enzyme pathway and/or the cyclooxygenase (prostaglandin synthetase) enzyme pathway. In preferred practice, the substituted N-hydroxy compound of the pharmaceutical composition is capable of inhibiting both the lipoxygenase and the cyclooxygenase enzyme pathways in the amount at which that substituted pyrazole compound is present in the pharmaceutical composition, when that composition is introduced as a unit dose into an appropriate mammal such as a laboratory rat.

The term "unit dosage" and its grammatical equivalent is used herein to refer to physically discrete units suitable as unitary dosages for human patients and other warm blooded animals, each unit containing a predetermined effective, pharmacologic amount of the active ingredient calculated to produce the desired pharmacological effect in association with the required physiologically tolerable carrier, e.g., a diluent or a vehicle. The specification for the novel unit dosage forms of this invention are dictated by and are directly dependent on (a) the unique characteristics of the active ingredient, and (b) the limitations inherent in the art of compounding such an active ingredient for therapeutic use in humans and other animals. Examples of suitable unit dosage forms in accord with this invention are tablets, capsules, pills, powder packets, granules, wafers, and the like, segregated multiples of any of the foregoing, as well as liquid solutions and suspensions.

The active ingredient is referred to herein as being dispersed in the carrier. Thus, the dispersion formed can be a simple admixture, a non-settling dispersion as in the case of certain emulsions, or as an ultimate dispersion, a true solution.

The amount of active ingredient that is administered in vivo depends on the age and weight of the mammal treated, the particular medical condition to be treated, the frequency of administration, and the route of administration. The dose range can be 0.01 to 500 milligrams per kilogram of body weight, more preferably 0.1 to 50 milligrams per kilogram of body weight and most preferably 0.1 to 25 milligrams per kilogram of body weight. The human adult dose is in the range of 10 to 2000 milligrams daily, given as a single dose or in 3 or 4 divided doses. Veterinary dosages correspond to human dosages with the amounts administered being in proportion to the weight of the animal as compared to adult humans.

As is seen from the data discussed hereinafter, orally administered unit doses containing 1 to 50 milligrams of a 2- and 3-substituted (1',5'-diaryl-3'-pyrazolyl)-N-hydroxypropanamide per kilogram of laboratory rat body weight (e.g., about 200 grams each) were useful in reducing inflammation. These results are contrary to those reported by Virmani et al., Indian J. Chem., Sect. B, 17:472-477 (1979) who reported compounds that are structurally similar to those described herein were not active as anti-inflammatory agents.

Physiologically tolerable carriers are well known in the art. Exemplary of liquid carriers are aqueous solutions that contain no material in addition to the substituted pyrazole compound, or contain a buffer such as sodium phosphate at physiological pH value, saline and the like.

Liquid compositions can also contain liquid phases in addition to and to the exclusion of water. Exemplary of such additional liquid phases are glycerin and vegetable oils such as cottonseed oil.

Exemplary solid carriers (diluent) include those materials usually used in the manufacture of pills or tablets, and include corn starch, lactose, dicalcium phosphate, thickeners such as tragacanth and methylcellulose U.S.P., finely divided SiO₂, polyvinylpyrrolidone, magnesium stearate and the like. Antioxidants such as methylparaben and propylparaben can be present in both solid and liquid compositions, as can sweeteners such as cane or beet sugar, sodium saccharin, sodium cyclamate and the dipeptide methyl ester sweetener sold under the trademark NUTRASWEET (aspartame) by G. D. Searle Co.

The composition is used to treat inflammatory conditions by administering an effective amount of a pharmaceutical composition that includes a unit dose of an active ingredient that is the before-described substituted N-hydroxypropanamide compound dispersed in a pharmaceutically acceptable carrier. The pharmaceutical composition is preferably maintained within the mammal until the substituted N-hydroxypropanamide compound is cleared from the mammal's body by natural means such as excretion or metabolism.

The pharmaceutical composition can be administered orally, topically or by injection, by means well known in the art. In preferred practice, the composition is administered orally as a tablet, capsule or aqueous dispersion.

5 Best Modes for Carrying Out the Invention

Melting points (mp) were determined on a Thomas-Hoover apparatus, and are uncorrected. Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with tetramethylsilane (TMS) as the internal standard on a Varian T-60A or an IBM WP-100 spectrometer. The values are expressed in parts per million downfield from TMS. EI and CI mass spectra were obtained on a
 10 Finnigan 1015D quadrupole mass spectrometer coupled to a Finnigan 9500 gas chromatograph or a Finnigan MAT 8230 Double Focusing high resolution mass spectrometer. In Tables 1-4 the elemental analysis for each compound was within $\pm 0.4\%$.

15 Example 1

Ethyl 5-(4-chlorophenyl)-1-(4-methoxyphenyl)pyrazole-3-carboxylate (1)

Ethyl 4-(4-chlorophenyl)-2,4-dioxobutanoate sodium salt (10.0 g, 36.1 mM), synthesized from 4-chloroacetophenone and diethyloxalate employing lithium diisopropylamide as base, and 4-methoxyphenyl-
 20 hydrazine hydrochloride (6.31 g, 36.1 mM) in cold absolute EtOH (360 ml) were stirred at 0° for 4 hr., at rt for 18 hr and then at reflux for 5 hr. The resulting solution was evaporated in vacuo, H₂O (100 ml) was added and the aqueous phase extracted with Et₂O (3 x 100 ml). The combined ether layer was washed (brine), dried (Na₂SO₄) and concentrated in vacuo to give a crude solid which by NMR was a 5:1 mixture of
 25 the title compound to the corresponding 1,3-diphenyl pyrazole. Recrystallization from EtOAc:hexane (2x) afforded pure 1 (7.93 g, 61%) as a white solid, mp = 107-108° C, MS, (DCI) m/e 357 (M+1).

Ethyl 4-(4-methoxyphenyl)-2,4-dioxobutanoate lithium salt (60.0 g, 0.23 M) synthesized from 4-methoxyacetophenone and diethyloxalate employing lithium hexamethyldisilazide as base, and 4-methoxyphenyl-
 30 hydrazine hydrochloride (44 g, 0.25 M) were combined in ethanol (2 l) and stirred at RT for 24 hr, concentrated in vacuo and crystallized to afford ethyl 1,5-bis (4-methoxyphenyl)pyrazole-3-carboxylate as a white solid, 75 g, 91% yield; mp = 97-98° C; MS, (m/e) 352 (M⁺).

35

| Anal. Calcd. for C ₂₀ H ₂₀ N ₂ O ₄ : | | | |
|--|------------------------|----------------------|---------------------|
| Found: | C, 68.17; C, 68.39; | H, 5.72; H, 5.75; | N, 7.95 N, 7.87. |

40 Example 2

Ethyl 1-(4-methoxyphenyl)-5-(4-methylphenyl)pyrazole-3-carboxylate (2)

Following the procedure of Example 1, but substituting 4'-methylacetophenone for 4-chloroacetophenone afforded the title compound 2 as a white solid, mp = 124-125°, MS, (DCI) m/e 337
 45 (M+1).

50

| Anal. Calcd. for C ₂₀ H ₂₀ N ₂ O ₃ : | | | |
|--|------------------------|----------------------|--------------------|
| Found: | C, 71.41; C, 71.13; | H, 5.99; H, 6.16; | N, 8.33 N, 8.36 |

55

Example 35-(4-Chlorophenyl)-3-hydroxymethyl-1-(4-methoxyphenyl) pyrazole (3)

5 A solution of compound 1 (9.1 g, 25.5 mM) in THF (50 ml) was added over 45 min to a stirred suspension of LiAlH₄ (0.726 g, 19.1 mM) in THF (50 ml) at 0°C and stirring continued for 1 hr. The suspension was diluted with Et₂O (100 ml) and H₂O (0.73 ml), 15% aq. NaOH (0.73 ml) and H₂O (2.1 ml) were added in sequence. The mixture was stirred for 16 hr, MgSO₄ added and the suspension stirred an additional hour, filtered and the solids washed with Et₂O. The combined organic layer was concentrated in
 10 vacuo, the residue dissolved in hot EtOAc and crystallized by the addition of hexane to give pure 3 (7.43 g, 93%) as a white solid, mp 95-97°C, MS, m/e 314 (M⁺).

| Anal. Calcd. for C ₁₇ H ₁₅ ClN ₂ O ₂ : | | | |
|--|-----------|----------|----------|
| | C, 64.87; | H, 4.88; | N, 8.90 |
| Found: | C, 64.75; | H, 4.83; | N, 8.84. |

Following the procedure of Example 3, but substituting ethyl 1,5-bis(4-methoxyphenyl)pyrazole-3-carboxylate for compound 1 afforded 3-hydroxymethyl-1,5-bis(4-methoxyphenyl)pyrazole (88) as a yellow foam,
 20 MS, (m/e) 310 (M⁺).

| Anal. Calcd. for C ₁₈ H ₁₈ N ₂ O ₃ · ½ H ₂ O: | | | |
|--|-----------|----------|---------|
| | C, 68.88; | H, 5.94; | N, 8.93 |
| Found: | C, 68.75; | H, 6.01; | N, 8.88 |

Example 4

30 3-Hydroxymethyl-1-(4-methoxyphenyl)-5-(4-methylphenyl) pyrazole (4).

Following the procedure for Example 3, but substituting compound 2 for compound 1 afforded the title compound 4 as a white solid, mp = 100-102°C, MS, m/e 294 (M⁺).

| Anal. Calcd. for C ₁₈ H ₁₈ N ₂ O ₂ : | | | |
|--|-----------|----------|---------|
| | C, 73.45; | H, 6.16; | N, 9.52 |
| Found: | C, 73.24; | H, 6.16; | N, 9.57 |

Example 5

45 3-Bromomethyl-5-(4-chlorophenyl)-1-(4-methoxyphenyl) pyrazole (5)

To a solution of compound 3 (3.14 g, 10 mM) in benzene (100 ml) was added PBr₃ (1.35 g, 5 mM) in benzene (10 ml) dropwise with stirring. The reaction mixture was refluxed 1 hr, cooled, poured into ice water (100 ml) and extracted with Et₂O (2 x 100 ml). The combined organic layer was washed with 10%
 50 NaHCO₃, dried (Na₂SO₄), filtered and concentrated to give a tan oil which crystallized on standing to afford compound 5, mp = 88-90°C, MS, (DCI) m/e 377 (M + 1).

Example 6

55 3-Bromomethyl-1-(4-methoxyphenyl)-5-(4-methylphenyl) pyrazole (6)

Following the procedure of Example 5, but substituting compound 4 for compound 3 afforded the title compound 6 which was recrystallized from CH₂Cl₂:hexane as a white solid, mp = 119-121°C.

| Anal. Calcd. for C ₁₈ H ₁₇ BrN ₂ O: | | | |
|--|-----------|----------|---------|
| | C, 60.52; | H, 4.80; | N, 7.84 |
| Found: | C, 60.61; | H, 4.97; | N, 7.57 |

Example 7

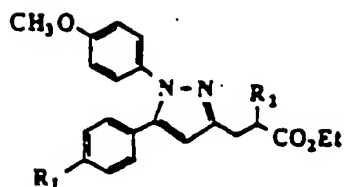
Ethyl 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-(4-chlorophenyl)propanoate (7)

NaH (3.12 g, 60% suspension in mineral oil, 78 mM) was suspended in anhydrous DMF (150 ml), cooled to 0°C and ethyl 4-chlorophenyl acetate (15.5 g, 78 mM) in DMF (150 ml) was added dropwise and the resulting solution stirred for 1 hr. Pyrazole bromide 5 (8.0 g, 21 mM) in DMF (150 ml) was added dropwise and the resulting reaction mixture allowed to warm to rt. The solvent was evaporated in vacuo, the residue dissolved in EtOAc (200 ml), washed with H₂O (4 x 100ml), dried (Na₂SO₄) and evaporated in vacuo to give a residue which was purified by flash chromatography on silica using 20% EtOAc:hexane as eluent to afford the title compound 7 as a yellow glass, 7.48 g (72% yield), MS, m/e 494 (M⁺).

| Anal. Calcd. for C ₂₇ H ₂₄ Cl ₂ N ₂ O ₃ : | | | |
|--|-----------|----------|---------|
| | C, 65.46; | H, 4.88; | N, 5.65 |
| Found: | C, 65.18; | H, 4.90; | N, 5.49 |

Following the procedure of Example 7, and using either pyrazole bromide 5 or 6 and substituting the appropriate aryl acetate for ethyl 4-chlorophenyl acetate afforded the compounds of Table 1.

Table 1



| Comp. | | | % | MS | |
|-------|-----------------|-----------------------|-------|----------------------|-------|
| No. | R ₁ | R ₂ | Yield | m/e(M ⁺) | C,H,N |
| 8 | Cl | Phenyl | 45 | 460 | X |
| 9 | Cl | 3,4-dimethoxyphenyl | 52 | 520 | X |
| 10 | Cl | 4-methoxyphenyl | 34 | 490 | X |
| 11 | CH ₃ | 2-naphthyl | 30 | 490 | X |
| 12 | CH ₃ | 1-naphthyl | 33 | 490 | X |
| 13 | CH ₃ | 2-methoxyphenyl | 61 | 470 | X |
| 14 | CH ₃ | 2-pyridyl | 49 | 441 | X |
| 15 | CH ₃ | 4-biphenyl | 31 | 516 | X |
| 16* | CH ₃ | 2-carboxymethylphenyl | 92 | 484 | X |
| 17 | CH ₃ | 3-pyridyl | 61 | 441 | X |

*Synthesized as the methyl ester rather than as the ethyl ester

Example 8

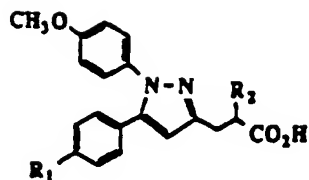
3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-(4-chlorophenyl) propanoic acid (18)

Compound 7 (7 g, 14.1 mM) was dissolved in a solution of 50% aq. KOH (4.74 g, 42.3 mM) in absolute EtOH (200 ml) and refluxed for 1.5 hr. The solvent was removed in vacuo and the solid residue dissolved in H₂O (250 ml), acidified to pH 4 with 4N HCl and extracted with EtOAc (300 ml). The organic layer was dried (Na₂SO₄), filtered and evaporated in vacuo to give a foam which was crystallized from CH₂Cl₂:hexane to give the title compound 18 (6.6 g) as a white solid, mp = 161.5-163 °C, MS, m/e 466 (M⁺).

| Anal. Calcd. for C ₂₅ H ₂₀ Cl ₂ N ₂ O ₃ : | | | |
|--|-----------|----------|---------|
| | C, 64.25; | H, 4.31; | N, 5.99 |
| Found: | C, 64.43; | H, 4.33; | N, 5.70 |

Following the procedure of Example 8, but substituting the compounds of Table 1 for compound 7 gave the compounds of Table 2.

Table 2



| Comp. | | | Melting | MS | |
|------------|----------------------|----------------------|--------------|---------------------------|--------------|
| <u>No.</u> | <u>R₁</u> | <u>R₂</u> | <u>Point</u> | <u>m/e(M⁺)</u> | <u>C,H,N</u> |
| 19 | Cl | 4-methoxyphenyl | 193-195° | 462 | X |
| 20 | Cl | 3,4-dimethoxyphenyl | 109-115° | 492 | X |
| 21 | CH ₃ | 2-naphthyl | 158-159.5° | 462 | X |
| 22* | CH ₃ | 1-naphthyl | >280° | 418 (M-44) | X |
| 23 | CH ₃ | 2-methoxyphenyl | 150-151° | 442 | X |
| 24 | CH ₃ | 4-biphenyl | 167-170° | 488 | X |
| 25** | CH ₃ | 2-carboxyphenyl | 204.5-205.5° | 438 (M-18) | X |

*Isolated as the sodium salt

**Prepared from compound 16

Example 9

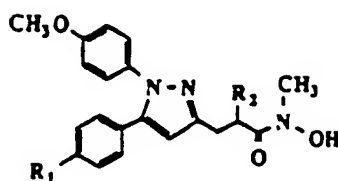
3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-(4-chlorophenyl)-N-hydroxy-N-methylpropanamide
(26)

Compound 18 (1.77 g, 3.8 mM) was suspended in CH₂Cl₂ (80 ml) and treated with oxalyl chloride (0.45 ml, 5.2 mM) to give a clear yellow solution which was allowed to reflux for 1 hr. The solvent was evaporated in vacuo to give the acyl chloride as a white semi-solid which was dissolved in CH₂Cl₂ (15 ml) and added dropwise to a solution of N-methylhydroxylamine·HCl (0.48 g, 5.7 mM), Et₃N (2.12 ml, 15.2 mM) and CH₂Cl₂ (15 ml) which was cooled to 0°C. The reaction was allowed to warm to rt and was stirred for 12 hours, washed with 5% aq. HCl (50 ml), dried (Na₂SO₄) and evaporated to give a crude semi-solid which was purified by flash chromatography on Silica (40% EtOAc:hexane) followed by recrystallization from CHCl₃:hexane to give the title compound 26 (1.15 g, 61%) as a white solid, mp = 113-117°C, MS, m/e 496 (M⁺).

| Anal. Calcd. for C ₂₆ H ₂₃ Cl ₂ N ₃ O ₃ : | | | |
|--|----------|---------|--------|
| | C,62.91; | H,4.67; | N,8.47 |
| Found: | C,62.50; | H,4.48; | N,8.32 |

Following the procedure of Example 9, but substituting the compounds of Table 2 for compound 18 gave the compounds of Table 3.

Table 3



| Comp. | | | Melting | MS | |
|------------|----------------------|----------------------|--------------|---------------------------|----------------|
| <u>No.</u> | <u>R₁</u> | <u>R₂</u> | <u>Point</u> | <u>m/e(M⁺)</u> | <u>C, H, N</u> |
| 27 | Cl | phenyl | 154-156° | 461 | X |
| 28 | Cl | 3,4-dimethoxyphenyl | 160-164° | 521 | X* |
| 29 | Cl | 4-methoxyphenyl | 158-159.5° | 491 | X |
| 30 | CH ₃ | 2-naphthyl | 173-175° | 491 | X |
| 31 | CH ₃ | 1-naphthyl | 140-142° | 491 | X** |
| 32 | CH ₃ | 2-methoxyphenyl | 144-146° | 471 | X |
| 33 | CH ₃ | 4-biphenyl | 139.5°-142 | 517 | X |

*1/2 hydrate

**1/4 hydrate

Example 10

6-(4-Chlorophenyl)-4,6-dioxo-2-spirocyclopentylhexanoic acid (34)

The general procedure described in ORTH 460 for the synthesis of 6-aryl-4,6-diketohexanoic acids was followed for the synthesis of compound 34. To a reaction vessel containing anhydrous THF (250 ml) and diisopropylamine (14 ml, 0.1 Mole) stirring under nitrogen at 0°C was added by syringe, n-BuLi (1.6 M, 62.5 ml, 0.1 Mole). The vessel was then cooled to -78°C. Alternatively, lithium hexamethyldisilazide (0.1 Mole) may be employed as the base in place of lithium diisopropylamide.

4-Chloroacetophenone (0.1 Mole) in anhydrous THF (50 ml) was added and the resulting solution allowed to stir for 30 minutes at -78°C and cyclopentane-1-carboxy-1-acetic acid anhydride* (6.16 g, 0.04 Mole) in THF (100 ml) was added via syringe. The solution was allowed to stir for 1 hr at -78°, warmed to rt for 1 hr and poured into 5% HCl (250 ml). The mixture was extracted with Et₂O (2 x 300 ml) and the combined ether extract was extracted with 10% NaOH (100 ml). The NaOH layer was separated and acidified with 4N HCl, and reextracted with Et₂O (2 x 300 ml). The combined ether layers were dried (Na₂SO₄), filtered and concentrated in vacuo. The resultant residue was chromatographed and recrystallized from CH₂Cl₂: hexane to give the title compound 34 and 6-(4-Chlorophenyl)-4,6-dioxo-3-spirocyclopentyl hexanoic acid (35). Compound 34; mp = 103-104.5°C, MS, m/e 308 (M⁺).

| Anal. Calcd. for C ₁₆ H ₁₇ O ₄ Cl: | | |
|---|-----------|---------|
| | C, 62.24; | H, 5.55 |
| Found: | C, 62.59; | H, 5.72 |

Compound 35; mp = 108-110°C, MS, m/e 308 (M⁺)

| Anal. Calcd. for C ₁₆ H ₁₇ O ₄ Cl: | | |
|---|-----------|---------|
| | C, 62.24; | H, 5.55 |
| Found: | C, 62.42; | H, 5.58 |

5

The following diketo acids were obtained following the procedure of Example 10 by substituting either cyclohexane-1-carboxy-1-acetic acid anhydride or cycloheptane-1-carboxy-1-acetic acid anhydride for cyclopentane-1-carboxy-1-acetic acid anhydride.

6-(4-Chlorophenyl)-4,6-dioxo-2-spirocyclohexylhexanoic acid (36).

6-(4-Chlorophenyl)-4,6-dioxo-3-spirocyclohexyl hexanoic acid (37).

6-(4-Chlorophenyl)-4,6-dioxo-2-spirocycloheptyl hexanoic acid (38).

6-(4-Chlorophenyl)-4,6-dioxo-3-spirocycloheptyl hexanoic acid (39).

Compound 36; MS, m/e 322 (M⁺); NMR (CDCl₃) δ 1.14-2.18 (10H, m), 2.73 (2H, s, C₃-H), 6.11 (1H, s), 7.26 (1H, s), 7.33-7.97 (4H, m).

Compound 37; NMR (CDCl₃) δ 1.08-2.10 (10H, m), 2.41 (2H, s, C₂-H), 6.32 (1H, s), 7.14 (1H, s), 7.33-7.93 (4H, m).

Compound 38; mp 135-136°C, MS, m/e 336 (M⁺).

20

| Anal. Calcd. for C ₁₈ H ₂₁ ClO ₄ : | | |
|---|-----------|---------|
| | C, 64.19, | H, 6.28 |
| Found: | C, 64.06, | H, 6.29 |

Compound 39; MS, m/e 336 (M⁺); NMR (CDCl₃) δ 1.3-2.2 (12H, m), 2.57 (2H, s, C₂-H), 6.28 (1H, s), 7.28 (1H, s), 7.34-7.94 (4H, m).

Example 11

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-2-spirocyclohexyl-N-methylpropanamide (40)

Compound 40 and the compounds of Table 4 were synthesized by the general procedure below described in ORTH 460.

A mixture of the appropriate 6-aryl-4,6-diketo-2-cycloalkyl-hexanoic acid (0.1 Mole) from Example 10 in methanol (750 ml) containing Et₃N (0.2 Mole) was treated with 4-methoxyphenylhydrazine hydrochloride (17.4 g, 0.1 Mole) at rt for 1 hr. If the reaction was incomplete at this point, it was refluxed until complete. The resulting darkened solution was evaporated in vacuo and taken up in Et₂O (700 ml); the ether solution was washed with aqueous 1N HCl (350 ml), brine, dried (Na₂SO₄), decolorized, evaporated in vacuo and recrystallized from Et₂O to give the crude pyrazole propionic acids.

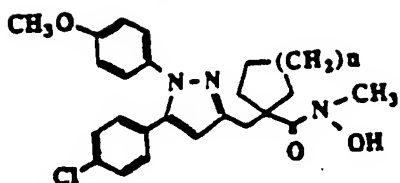
To a solution of the above acid(s) (2.77 mM) in tetrahydrofuran (20 ml) at 0°C, was added one drop of dimethyl formamide and oxalyl chloride (0.29 ml, 33 mM). After 0.5 hr the cooling bath was removed and stirring was continued for an additional 0.5 hr. The reaction mixture was concentrated in vacuo to remove any excess oxalyl chloride, and the acid chloride was taken up into THF (10 ml).

To a solution of methylhydroxylamine hydrochloride (0.35 g, 4.16 mM) and triethylamine (Et₃N) (1.55 ml, 11.10 mM) in THF, H₂O (10 ml:5 ml) at 0°C, was added the THF solution of the acid chloride dropwise over a 5 minute period. The cooling bath was removed, and the reaction mixture was stirred for 1 hr, diluted to 100 ml with EtOAc, washed with H₂O, dried (MgSO₄), filtered, and concentrated in vacuo. Chromatography (silica gel) of the residue with EtOAc as eluent, followed by recrystallization from CH₂Cl₂: hexane gave the compounds of Table 4.

55

*Synthesized according to Scott, K. R. et al., J. of Pharm. Sci., 72, 183 (1983), see also I. Vogel, J. Chem. Soc. 2010, 1928.

Table 4



| Compound | | Melting | MS | |
|--------------|---|----------|-----------------------|---------|
| # | n | Point | m/e (M ⁺) | C, H, N |
| 40 | 2 | 150-151° | 453 | X |
| 41 | 1 | foam | 439 | X* |
| 42 | 3 | 149-151° | 467 | X** |
| *1/2 hydrate | | | | |
| **hydrate | | | | |

Following the procedure of Example 11, but substituting compounds 35, 37 or 39 for the 6-aryl-4,6-diketo-2-cycloalkyl-hexanoic acid gave the corresponding 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-2-spirocycloalkyl-N-methylpropanamide.

Example 12

6-(4-Chlorophenyl)-2,2-dimethyl-4,6-dioxohexanoic acid (43)

Following the procedure of Example 10, but substituting 2,2-dimethyl succinic anhydride for cyclopentane-1-carboxy-1-acetic acid anhydride and carrying out the reaction on 0.5 times the scale afforded a crude oil which upon recrystallization from Et₂O (3x) afforded the title compound 43, mp = 137-139°C, MS, m/e 282 (M⁺).

| Anal. Calcd. for C ₁₄ H ₁₅ ClO ₄ : | | |
|---|-----------|---------|
| | C, 59.47; | H, 5.35 |
| Found: | C, 59.25; | H, 5.21 |

The mother liquors from above contained the corresponding 6-(4-chlorophenyl)-3,3-dimethyl-4,6-dioxohexanoic acid (44) as the major component.

Example 13

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-2,2,N-trimethylpropanamide (47)

Following the procedure of Example 11, and employing the isomeric mixture of geminal dimethyl diones 43 and 44 obtained in Example 12 afforded a mixture of four isomeric propionic acids which were separated by chromatography to afford 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2,2-dimethyl propionic acid (45), NMR (DMSO-d₆) δ 2.8 (s, C₃-H); MS, m/e 384 (M⁺), and 3-[3-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-pyrazolyl]-2,2-dimethyl propionic acid (46), mp = 172-174°, MS, m/e 384 (M⁺).

| Anal. Calcd. for $C_{21}H_{21}ClN_2O_3$: | | | |
|---|-----------|----------|---------|
| | C, 65.54; | H, 5.50; | N, 7.28 |
| Found: | C, 65.48; | H, 5.52; | N, 7.40 |

The corresponding 3,3-dimethyl propionic acid analogs of compounds 45 and 46 were shown to be present (NMR) but were not purified.

A mixture of the 4 isomeric propionic acids was then converted to the corresponding N-methyl hydroxamic acids following the procedure described in Example 11. The crude product, which was shown (NMR) to contain 4 isomeric N-methyl hydroxamic acids, upon flash chromatography on Silica gave the title compound 47 as a yellow foam; NMR ($CDCl_3$) δ 3.05 (s, 2H, C_3 -H), 6.33 (s, 1H, C_4 -H); MS, m/e 413 (M^+).

| Anal. Calcd. for $C_{22}H_{24}ClN_3O_3$: | | | |
|---|-----------|----------|----------|
| | C, 63.84; | H, 5.85; | N, 10.15 |
| Found: | C, 63.56; | H, 5.91; | N, 9.89 |

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-3,3,N-trimethylpropanamide (48) was obtained by chromatography as a yellow foam, NMR ($CDCl_3$) δ 2.89 (s, 2H, C_2 -H), 6.38 (s, 1H, C_4 -H); MS, m/e 413 (M^+).

| Anal. Calcd. for $C_{22}H_{24}ClN_3O_3$: | | | |
|---|-----------|----------|----------|
| | C, 63.84; | H, 5.85; | N, 10.15 |
| Found: | C, 63.78; | H, 5.81; | N, 10.02 |

Example 14

Sodium 1-(4-chlorophenyl)-4-methyl-6-hydroxyhexane-1,3-dionate (49a)

4-Chloroacetophenone (15.4 g, 0.1 mole) was added to LDA (0.1 mol) in THF (400 ml) at $-78^\circ C$ under nitrogen. The resulting solution was stirred for 15 minutes and 2-methylbutyrolactone (5 g, 0.05 moles) in THF (20 ml) was added by syringe and the reaction kept at $-78^\circ C$ for 1 hr and then at rt for 2 hr. The reaction mixture was poured into 5% HCl (150 ml) and extracted with ether, the ether layer was treated with 1 NaOH and the resulting solid, the title compound 49, was filtered (4 g, 29%) as a white solid, mp = $135-140^\circ C$.

| Anal. Calcd. for $C_{13}H_{14}ClNaO_3$: | | |
|--|-----------|---------|
| | C, 56.43; | H, 5.10 |
| Found: | C, 56.12; | H, 5.28 |

The NaOH layer from above was then acidified with HCl and extracted with ether, the ether layer dried (Na_2SO_4) and evaporated in *vacuo* to give a yellow semi-solid (3.6 g, 28%) which was 1-(4-chlorophenyl)-4-methyl-6-hydroxyhexane-1,3-dione (49b).

Example 15

5-(4-Chlorophenyl)-3-(3-hydroxy-1-methylpropyl)-1-(4-methoxy phenyl)pyrazole (50)

Following the procedure described in Example 11, but employing 49b (2.54 g, 0.01 mole) as the diketo component afforded the title compound 50 as a white solid (1.1 g, 31%, Recry./ Et_2O), mp = $97.5-98.5^\circ$; MS, m/e 356 (M^+).

| Anal. Calcd. for $C_{20}H_{21}ClN_2O_2$: | | | |
|---|-----------|----------|----------|
| | C, 67.31; | H, 5.93; | N, 7.85 |
| Found: | C, 67.22; | H, 6.30; | 5N, 7.85 |

5

Example 16

10 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-3,N-dimethyl-N-hydroxypropanamide Hemihydrate - (51)

To a solution of compound 50 (0.65 g, 1.8 mM) in acetone (50 ml) was added Jones Reagent (1.85 ml, 3.7 mM) and the reaction stirred for 1.5 hr, the acetone decanted and the chromium residues washed exhaustively with acetone. The combined acetone layers were then evaporated in vacuo, the residue
 15 dissolved in EtOAc (100 ml), washed (H_2O), dried (Na_2SO_4) and concentrated to give an oil which was chromatographed on Silica (EtOAc/MeOH, 30% as eluent) to afford 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-3-methylpropanoic acid (0.62 g, 92%) as a yellow semi-solid which was used without further purification and following the procedure of Example 11 was converted to the title hydroxamic acid 51
 20 as a yellow foam (92%); NMR ($CDCl_3$) δ 1.50 (d, 3H, J = 7Hz, C_3-CH_3); MS, m/e 399 (M^+).

20

| Anal. Calcd. for $C_{21}H_{22}ClN_3O_3 \cdot 1/2H_2O$: | | | |
|---|-----------|----------|----------|
| | C, 61.68; | H, 5.67; | N, 10.27 |
| Found: | C, 61.72; | H, 5.58; | N, 9.82 |

25

Example 17

30 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2,N-dimethyl-N-hydroxy propanamide Hemihydrate - (52)

Following the procedure described in Example 14, but substituting 3-methylbutyrolactone for 2-methylbutyrolactone and employing the resulting product as the starting material for Examples 15 and 16
 35 afforded the title compound 52 as a yellow foam (93%); NMR ($CDCl_3$) δ 1.25 (d, 3H, J = 7Hz, C_2-CH_3); MS, m/e 399 (M^+).

35

| Anal. Calcd. for $C_{21}H_{22}ClN_3O_3 \cdot 1/2H_2O$: | | | |
|---|-----------|----------|----------|
| | C, 61.68; | H, 5.67; | N, 10.27 |
| Found: | C, 61.97; | H, 5.72; | N, 10.00 |

40

Example 18

45

1-(4-Chlorophenyl)-3-(2-carboxyphenyl)propane-1,3-dione (53)

Following the general procedure described in Example 10 but substituting phthalic anhydride for cyclopentane-1-carboxy-1-acetic acid anhydride afforded the title compound as a white solid, mp = 148-150°C, MS, m/e 302 (M^+).

50

| Anal. Calcd. for $C_{16}H_{11}ClO_4$: | | |
|--|-----------|---------|
| | C, 63.48; | H, 3.66 |
| Found: | C, 63.33; | H, 3.61 |

55

Likewise when cis-1,2-cyclohexane dicarboxylic anhydride; trans-1,2-cyclohexanedicarboxylic anhydride; cis-1,2,3,6-tetrahydrophthalic anhydride; 3,4,5,6-tetrahydrophthalic anhydride; 3,6-Endoxo-1,2,3,6-tetrahydrophthalic anhydride or 2,3-pyridinedicarboxylic anhydride were substituted for phthalic anhydride the following diketo acids were obtained.

- 5 cis-1-[1-(4-Chlorophenyl)-1,3-dioxoprop-3-yl]cyclohexane -2-carboxylic acid (54), white solid, mp = 158-160 °C; MS, m/e 308 (M⁺).

10

| Anal. Calcd. for C ₁₆ H ₁₇ ClO ₄ : | | |
|---|-----------|---------|
| | C, 62.24; | H, 5.55 |
| Found: | C, 62.06; | H, 5.77 |

15

- trans-1-[1-(4-Chlorophenyl)-1,3-dioxoprop-3-yl]cyclohexane-2-carboxylic acid (55), white solid; mp = 177-180 °C; MS, m/e 308 (M⁺).

20

| Anal. Calcd. for C ₁₆ H ₁₇ ClO ₄ : | | |
|---|-----------|---------|
| | C, 62.24; | H, 5.55 |
| Found: | C, 62.02; | H, 5.71 |

25

- cis-1-[1-(4-Chlorophenyl)-1,3-dioxoprop-3-yl]-cyclohex-4-ene-2-carboxylic acid (56), yellow crystalline solid, mp = 132-135 °C; MS, m/e 306 (M⁺).

30

- 1-[3-(4-Chlorophenyl)-1,3-dioxopropyl]-2-carboxycyclohex-1-ene (57), white solid, mp = 171-172 °C; MS, m/e 306 (M⁺).

35

| Anal. Calcd. for C ₁₆ H ₁₅ ClO ₄ : | | |
|---|-----------|---------|
| | C, 62.65; | H, 4.92 |
| Found: | C, 62.25; | H, 4.95 |

40

- cis-1-[1-(4-Chlorophenyl)-1,3-dioxoprop-3-yl]-6-carboxy-2,5-endoxo-3,4-cyclohexene (58), white solid, mp = 108-109 °C; MS, m/e 320 (M⁺).

45

| Anal. Calcd. for C ₁₆ H ₁₃ ClO ₅ : | | |
|---|-----------|---------|
| | C, 59.92; | H, 4.09 |
| Found: | C, 60.12; | H, 4.13 |

50

- 1-(4-Chlorophenyl)-3-(6-carboxypyrid-2-yl)propan-1,3-dione (59), yellow solid, mp = 183-185 °C; MS, m/e 303 (M⁺).

55

| Anal. Calcd. for C ₁₅ H ₁₀ ClNO ₄ : | | | |
|--|-----------|----------|---------|
| | C, 59.32; | H, 3.32; | N, 4.61 |
| Found: | C, 59.00; | H, 3.22; | N, 4.57 |

In addition, when 4-methylacetophenone is substituted for 4-chloroacetophenone in Example 10 and either phthalic anhydride or cis-1,2-cyclohexanedicarboxylic anhydride is employed as the anhydride the following compounds are obtained.

1-(4-Methylphenyl)-3-(2-carboxyphenyl)propane-1,3-dione (60), white solid, mp=155-157°; MS, m/e 282 (M⁺).

| Anal. Calcd. for C ₁₇ H ₁₄ O ₄ : | | |
|---|-----------|---------|
| | C, 72.33; | H, 5.00 |
| Found: | C, 72.41; | H, 5.01 |

cis-1-[1-(4-Methylphenyl)-1,3-dioxoprop-3-yl] cyclohexane-2-carboxylic acid (61), white solid, mp = 144-147°; MS, m/e 288 (M⁺).

| Anal. Calcd. for C ₁₇ H ₂₀ O ₄ : | | |
|---|-----------|---------|
| | C, 70.81; | H, 6.99 |
| Found: | C, 70.39; | H, 7.23 |

Example 19

2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)pyrazol-3-yl]-N-hydroxy-N-methylbenzamide Hemihydrate (62)

Following the procedure of Example 11 but employing 1-(4-Chlorophenyl)-3-(2-carboxyphenyl)propane-1,3-dione as the diketo acid afforded the title compound 62 as a white foam, MS, m/e 433 (M⁺).

| Anal. Calcd. for C ₂₄ H ₂₀ N ₃ O ₃ • 1/2H ₂ O: | | | |
|---|-----------|----------|---------|
| | C, 65.09; | H, 4.77; | N, 9.48 |
| Found: | C, 64.66; | H, 4.63; | N, 9.13 |

Likewise, following the procedure of Example 11 but employing the diketo acids described in Example 18 afforded the following compounds.

cis-2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-1-(N-hydroxy-N-methyl)carboxamidocyclohexane (63), white solid, mp = 143-145 °C, MS, m/e 439 (M⁺).

| Anal. Calcd. for C ₂₄ H ₂₆ ClN ₃ O ₃ : | | | |
|--|-----------|----------|---------|
| | C, 65.52; | H, 5.96; | N, 9.55 |
| Found: | C, 65.26; | H, 6.20; | N, 9.29 |

cis-2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-1-(N-hydroxy-N-methyl)-carboxamidocyclohex-4-ene Hemihydrate (64), white foam, NMR (CDCl₃ δ 3.1 (s, 3H, NCH₃); MS, m/e 437 (M⁺).

| Anal. Calcd. for C ₂₄ H ₂₄ ClN ₃ O ₃ : | | | |
|--|-----------|----------|---------|
| | C, 64.49; | H, 5.63; | N, 9.40 |
| Found: | C, 64.76; | H, 5.57; | N, 9.06 |

Epimerization of compound 64 in base afforded trans-2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-1-(N-hydroxy-N-methyl) carboxamidocyclohex-4-ene Hemihydrate (65), white foam, NMR (CDCl₃) δ 3.3 (d, 3H, NCH₃); MS, m/e 437 (M⁺).

| Anal. Calcd. for $C_{24}H_{24}ClN_3O_3$: | | | |
|---|-----------|----------|---------|
| | C, 64.49; | H, 5.63; | N, 9.40 |
| Found: | C, 64.35; | H, 5.58, | N, 9.42 |

cis-1-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-6-(N-hydroxy-N-methyl)carboxamido-2,5-endoxo-3,4-cyclohexene (66), white solid, mp = 108-110 °C, MS, m/e 451 (M^+).

| Anal. Calcd. for $C_{24}H_{22}ClN_3O_4$: | | | |
|---|-----------|----------|---------|
| | C, 63.79; | H, 4.91; | N, 9.30 |
| Found: | C, 63.37; | H, 4.96; | N, 9.13 |

2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-3-(N-hydroxy-N-methylcarboxamido)pyridine (67), tan solid, mp = 172-175 °C, MS, m/e 434 (M^+).

| Anal. Calcd. for $C_{23}H_{19}ClN_4O_3$: | | | |
|---|-----------|----------|----------|
| | C, 63.52; | H, 4.40; | N, 12.88 |
| Found: | C, 63.40; | H, 4.48; | N, 12.81 |

2-[5-(4-Methylphenyl)-1-(4-methoxyphenyl)pyrazol-3-yl]-N-hydroxy-N-methylbenzamide Hemihydrate (68), white solid, mp = 134-136 °C, MS, m/e 413 (M^+).

| Anal. Calcd. for $C_{25}H_{23}N_3O_3 \cdot 1/2H_2O$: | | | |
|---|-----------|----------|---------|
| | C, 71.07; | H, 5.72; | N, 9.94 |
| Found: | C, 71.20; | H, 5.49; | N, 9.86 |

cis-2-[5-(4-Methylphenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-1-(N-hydroxy-N-methyl)-carboxamidocyclohexane (69)

2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-1-(N-hydroxy-N-methyl)carboxamido-cyclohex-1-ene (70)

Example 20

3-Allyl-2,4-dimethoxyphenyl-1-yl-4-methoxyphenylhydrazone Hemihydrate (71)

To a solution of 3-allyl-2,4-dihydroxyacetophenone [28.45 g, 0.148 mole; synthesized as described in J. Chem. Soc., pg. 628 (1935)] in acetone (800 ml) was added potassium carbonate (442 g). The resulting slurry was treated with iodomethane (89 ml) at reflux for 6 hr, cooled and filtered, and the filtrate evaporated in vacuo and the crude product obtained was combined with that of an identical run and purified by flash chromatography on Silica to give 3-allyl-2,4-dimethoxyacetophenone (21.3 g), NMR ($CDCl_3$) δ 3.73, 3.9 (2s, 3H each, 2-, 4- OCH_3); MS, m/e 206 (M^+).

A solution of 3-allyl-3,4-dimethoxyacetophenone (21.3 g, 97 mM) in EtOH (48.8 ml) and glacial Acetic Acid (3.25 ml) was treated with 4-methoxyphenylhydrazine (13.36 g, 97 mM) and heated at 35 °C for 1 hr and then allowed to stand at rt for 18 hr and the resulting solids filtered and washed with pet ether to afford pure 71 (15.04 g, 46%) as a yellow solid, mp = 49-50 °C, MS, m/e 340 (M^+).

| Anal. Calcd. for $C_{20}H_{24}N_2O_3 \cdot 1/2H_2O$: | | | |
|---|-----------|----------|---------|
| | C, 68.74; | H, 7.21; | N, 8.02 |
| Found: | C, 68.47; | H, 7.17; | N, 7.69 |

Example 213-(3-Allyl-2,4-dimethoxyphenyl)-5-(4-chlorophenyl)-1-(4-methoxyphenyl)pyrazole (72)

5 A solution of compound 71 (12.26 g, 36 mM) in anhydrous THF (140 ml) was cooled to -10 °C under nitrogen and treated with *n*-BuLi (72 mM) to afford the dilithio anion which was allowed to stir at 0 °C for 0.5 hr. Methyl 4-chlorobenzoate (3.07 g, 18 mM) in THF (10 ml) was added to the above dianion and the reaction mixture stirred at 0 °C for 15 min, then neutralized with 3N HCl to a pH of 7.5, refluxed for 1 hr and stirred at rt for 21 hr. The reaction mixture was evaporated *in vacuo* to give a brown oil which was dissolved in Et₂O, washed (H₂O), dried and evaporated to give a dark brown oil which was purified by flash chromatography on Silica and crystallized from pet ether to give the title compound 72 (2.0 g, 24%) mp = 44-46 °C, MS, m/e 460 (M⁺).

15

| Anal. Calcd. for C ₂₇ H ₂₅ ClN ₂ O ₃ : | | | |
|--|-----------|----------|---------|
| | C, 70.35; | H, 5.47; | N, 6.08 |
| Found: | C, 70.48; | H, 5.62; | N, 5.91 |

20

Example 225-(4-Chlorophenyl)-3-[2,4-dimethoxy-3-(3-hydroxypropyl) phenyl]-1-(4-methoxyphenyl)pyrazole (73)

25 A slurry of compound 72 (6.82 g, 14.8 mm) in hexane was cooled to -10 °C under N₂ and treated with borane-methyl sulfide complex (10 mM) at 0 °C over a 0.5 hr period and then the reaction mixture refluxed gently for 2 hr, cooled and treated with 95% EtOH (12.75 ml) and 3N NaOH (1.59 ml) and cooled to 0 °C, followed by the dropwise addition of 30% H₂O₂ (1.91 ml) and the refluxed for 0.5 hr, cooled and poured into ice water. The resulting solid was filtered to give crude alcohol (6.25 g) which was purified via flash column chromatography on Silica and recrystallization from Et₂O/pet ether to afford pure 73 (2.89 g) as a yellow solid, mp = 152-153 °C; MS, m/e 478 (M⁺).

35

| Anal. Calcd. for C ₂₇ H ₂₇ ClN ₂ O ₄ : | | | |
|--|-----------|----------|---------|
| | C, 67.70; | H, 5.68; | N, 5.85 |
| Found: | C, 67.95; | H, 5.94; | N, 5.73 |

Example 23

40

3-[3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)pyrazol-3-yl]-2,6-dimethoxyphenyl] propionic acid (74)

Following the procedure of Example 16, but substituting compound 73 for compound 50 afforded the title compound 74 as a white solid, mp = 100-101 °C, MS, m/e 492 (M⁺).

45

Example 243-[3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)pyrazol-3-yl]-2,6-dimethoxyphenyl]-N-hydroxy-N-methylpropanamide (75)

50

Following the procedure described in Example 11 for hydroxamic acid synthesis but employing compound 74 as the starting propionic acid afforded the title compound 75 which crystallized from EtOAc: hexane as a white solid with 0.5 mole of EtOAc as solvate, mp = 90-92 °C, MS, m/e 521 (M⁺).

55

| Anal. Calcd. for $C_{28}H_{28}ClN_3O_5 \cdot 1/2C_4H_8O_2$: | | | |
|--|-----------|----------|---------|
| | C, 63.65; | H, 5.70; | N, 7.42 |
| Found: | C, 63.89; | H, 5.94; | N, 7.26 |

Example 25

1-(4-Methoxyphenyl)-5-(4-methylphenyl)pyrazol-3-yl carboxaldehyde (76)

Pyridine (54.6 ml, 0.68 M) was dissolved in CH_2Cl_2 (450 ml), cooled to 0 °C and CrO_3 (33.8 g) was added with stirring. Compound 4 (17.68 g, 56.3 mM) dissolved in CH_2Cl_2 (350 ml) was added to the mixture with stirring and kept at 0 °C for 30 min, then warmed to RT for 7 hr. The solvent was decanted and filtered through Florisil. The residual black tar was sonicated with EtOAc (3x) and the combined organic layer was evaporated in vacuo to give a brown oil which was dissolved in Et_2O , washed with 10% NaOH, 4N HCl and saturated brine, dried (Na_2SO_4), filtered and evaporated in vacuo to give a tan solid which upon recrystallization from Et_2O :hexane afforded the title compound 76 as a white solid (14.5 g, 83%) mp = 84-86 °.

Following the procedure of Example 25, but substituting 3-hydroxymethyl-1,5- bis(4-methoxyphenyl)-pyrazole, compound 88, for 3-hydroxymethyl-1-(4-methoxyphenyl)-5-(4-methylphenyl)pyrazole afforded 1,5-bis(4-methoxyphenyl)pyrazole- 3-aldehyde, compound 89 as a white solid, mp 113-115 °C, MS, m/e 308 (M^+).

| Anal. Calcd. for $C_{18}H_{16}N_2O_3$: | | | |
|---|-----------|----------|----------|
| | C, 70.12; | H, 5.23; | N, 9.09 |
| Found: | C, 70.06; | H, 5.21; | N, 9.04. |

Example 26

1-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-1-phenyl-methanol (77)

Compound 76 (2.92 g, 10 mM) was dissolved in THF (100 ml) and cooled to 0 °C. Phenylmagnesium bromide (11 mM) was added by syringe and after 1 hr the reaction was quenched with saturated NH_4Cl (50 ml). Et_2O (150 ml) was added and the organic layer was separated, washed (brine), dried (Na_2SO_4), filtered and evaporated in vacuo to afford the title compound 77 as a tan solid, mp = 101-103 °; MS, m/e 370 (M^+).

| Anal. Calcd. for $C_{24}H_{22}N_2O_2$: | | | |
|---|-----------|----------|---------|
| | C, 77.81; | H, 5.99; | N, 7.56 |
| Found: | C, 77.67; | H, 6.13; | N, 7.34 |

In a similar manner, substituting 4-fluorophenylmagnesium bromide for phenylmagnesium bromide affords 1-(4-fluorophenyl)-1-[1-(4-methoxyphenyl)-5- (4-methylphenyl)-3-pyrazolyl] methanol 78 as a yellow foam; MS, m/e 388 (M^+).

| Anal. Calcd. for $C_{24}H_{21}FN_2O_2$: | | | |
|--|-----------|----------|---------|
| | C, 74.20; | H, 5.45; | N, 7.21 |
| Found: | C, 73.80; | H, 5.29; | N, 7.17 |

In addition, substituting the appropriate arylmagnesium halide for phenylmagnesium bromide and employing either aldehyde 76 or 89 (Procedure A) afforded compounds of Table 5. Alternatively, substituting the appropriate aryl halide or the appropriately activated substituted aryl compound for phenylmagnesium bromide and subsequent treatment with butyl lithium at -78 °C followed by addition of aldehyde 76

or 89 (Procedure B) afforded the remaining compounds of Table 5.

Example 27

5 3-Benzoyl-1-(4-methoxyphenyl)-5-(4-methylphenyl)pyrazole (79)

Compound 77 (3.7 g, 10 mM) was dissolved in CH₂Cl₂ (100 ml) and pyridinium chlorochromate (3.44 g, 16 mM) was added with vigorous stirring and stirred for 30 min. Et₂O (150 ml) was added and the mixture was sonicated for 5 min and filtered through florisil (100-200 mesh), the Florisil washed with additional Et₂O
10 and the combined Et₂O layer evaporated in vacuo to yield the title compound of sufficient purity for subsequent steps.

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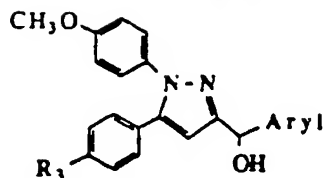
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Table 5



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| Compound # | R ₃ | Aryl | Melting Point | MS (m/e)M ⁺ | Pro-cedure | C,H,N |
|------------|----------------|-------------------------|---------------|------------------------|------------|-------|
| 90 | Me | 4-Biphenyl | 135-137° | 446 | A | X |
| 91 | Me | 4-Chlorophenyl | 130-132° | 404 | A | X |
| 92 | Me | 4-Tolyl | 138-140° | 384 | A | X |
| 93 | Me | 1-Naphthyl | 156-159° | 420 | A | X* |
| 94 | Me | 2-Naphthyl | 142-143.5° | 420 | A | X |
| 95 | Me | 4-Methoxyphenyl | 109-110.5° | 400 | B | X |
| 96 | Me | 2-Thienyl | 134-136° | 376 | B | X |
| 97 | Me | 2-Methoxyphenyl | 109-111° | 400 | B | X |
| 98 | Me | 6-Methoxy-2-naphthyl | 170.5-172.5° | 450 | B | X** |
| 99 | Me | 2-Furyl | 127-130° | 360 | B | X |
| 100 | OMe | 4-Tolyl | 138-139° | 400 | A | X |
| 101 | OMe | 4-Chlorophenyl | 155-156° | 420 | A | X |
| 102 | OMe | 4-Methoxyphenyl | 148-149° | 416 | B | X |
| 103 | OMe | 2-Methoxy-5-bromophenyl | foam | 495 | B*** | X |
| 104 | OMe | 2-Methoxyphenyl | foam | 416 | B | X |
| 105 | OMe | Phenyl | 103-106° | 386 | A | X |
| 106 | OMe | 2,3-Dimethoxyphenyl | foam | 446 | B | X |

*1/2 hydrate

**1/4 hydrate

***By-product in synthesis of compound 102

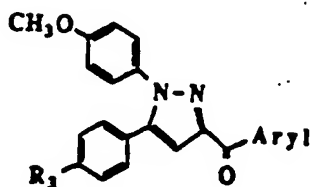
Recrystallization from Et₂O affords 79 as a white solid, mp = 166-167°; MS, m/e 368 (M⁺).

| Anal. Calcd. for C ₂₄ H ₂₀ N ₂ O ₂ : | | | |
|--|-----------|----------|---------|
| | C, 78.24; | H, 5.47; | N, 7.60 |
| Found: | C, 77.93; | H, 5.29; | N, 7.63 |

In a similar manner, substituting compound 78 for 77 afforded 3-(4-fluorobenzoyl)-1-(4-methoxyphenyl)-5-(4-methylphenyl) pyrazole (80) as a white solid, mp = 138-139°; MS, m/e 386 (M⁺).

In addition, substituting the appropriate alcohol from Table 5 for compound 77 afforded the compounds of Table 6.

Table 6



| Compound # | R ₃ | Aryl | Melting Point | MS (m/e)M ⁺ | C,H,N |
|------------|----------------|----------------------|---------------|------------------------|-------|
| 107 | Me | 4-Biphenyl | 146-148° | 444 | X |
| 108 | Me | 4-Chlorophenyl | 157-158.5° | 402 | X |
| 109 | Me | 4-Tolyl | 136-138° | 382 | X |
| 110 | Me | 1-Naphthyl | 158-159.5° | 418 | X |
| 111 | Me | 2-Naphthyl | 158.5-159.5° | 418 | X |
| 112 | OMe | 4-Tolyl | 137-138° | 398 | X |
| 113 | OMe | 4-Chlorophenyl | 145-147° | 418 | X |
| 114 | Me | 2-Thienyl | 161-162° | 374 | X |
| 115 | Me | 4-Methoxyphenyl | 127-128° | 398 | X |
| 116 | OMe | 4-Methoxyphenyl | 138-139° | 414 | X |
| 117 | Me | 2-Methoxyphenyl | 141-143° | 398 | X |
| 118 | OMe | 2-Methoxyphenyl | foam | 414 | X |
| 119 | Me | 6-Methoxy-2-naphthyl | 175-176° | 448 | X |
| 120 | Me | 2-Furyl | 139.5-141° | 358 | X |
| 121 | OMe | 2,3-Dimethoxyphenyl | foam | 444 | X |

Example 28

(E)-Ethyl-3-{1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl}-3-phenyl-2-propenoate (81) and the corresponding (Z) isomer (82)

Triethylphosphonoacetate (2.24 g, 10 mM) was dissolved in anhydrous THF (80 ml), cooled to -78°C and n-BuLi (10 mM) was added by syringe and the resulting colorless solution stirred 45 min. Compound 79 (3.68 g, 10 mM) in THF (80 ml) was added by syringe, the resulting solution stirred at -78° for 15 min, warmed to RT and then allowed to reflux for 8 hr under a N₂ atmosphere. The reaction was cooled to RT, partitioned between Et₂O and 5% HCl, and the Et₂O layer washed with brine, dried (Na₂SO₄) and evaporated in vacuo to give an oil which was chromatographed on Silica (Hexane:15% EtOAc) to afford a 3:2 mixture of 81:82.

Compound 81, oil, NMR (CDCl₃) δ 6.35 (s, 1H) 6.53 (s, 1H).

Compound 82, white solid, mp = 143-144°; NMR (CDCl₃) δ 6.18 (s, 1H) 6.85 (s, 1H).

| Anal. Calcd. for C ₂₈ H ₂₆ N ₂ O ₃ : | | | |
|--|-----------|----------|---------|
| | C, 76.69; | H, 5.98; | N, 6.39 |
| Found: | C, 76.82; | H, 6.00; | N, 6.48 |

5

Following the above procedure but substituting Compound 80 for 79 afforded (E)-Ethyl 3-(4-fluorophenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-2-propenoate (83) and the corresponding (Z)-isomer (84).

10

Compound 83, oil, NMR (CDCl₃) δ 6.30 (s, 1H), 6.55 (s, 1H).

Compound 84, mp = 132-133° (prisms); NMR (CDCl₃) δ 6.20 (s, 1H), 6.88 (s, 1H).

| Anal. Calcd. for C ₂₈ H ₂₅ FN ₂ O ₃ : | | | |
|---|-----------|----------|---------|
| | C, 73.67; | H, 5.52; | N, 6.14 |
| Found: | C, 74.04; | H, 5.53; | N, 6.25 |

15

Following the procedure of Example 28, but substituting the appropriate ketone of Table 6 for compound 79 afforded the compounds of Table 7. The E and Z isomers were separated by flash chromatography on Silica.

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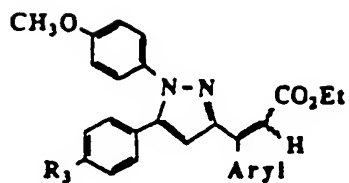
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55

Table 7



| Compound # | R ₃ | Aryl | E/Z Isomers | Melting Point | MS (m/e)M ⁺ | C.H.N |
|---------------|----------------|-----------------|------------------|------------------|---------------------------|-------|
| | | | | | | |
| 122 | OMe | 4-tolyl | E | foam | 468 | X |
| 123 | OMe | 4-tolyl | Z | 211-214° | 468 | X |
| 124 | Me | 4-tolyl | E | foam | 452 | X |
| 125 | Me | 4-tolyl | Z | 118-119° | 452 | X |
| 126 | OMe | 4-chlorophenyl | E | foam | 488 | X |
| 127 | OMe | 4-chlorophenyl | Z | 126-127° | 488 | X |
| 128 | Me | 4-chlorophenyl | Z | 141-143° | 472 | X |
| 129 | Me | 4-chlorophenyl | E | foam | 472 | X |
| 130 | OMe | 4-methoxyphenyl | E | foam | 484 | X |
| 131 | OMe | 2-methoxyphenyl | E/Z ^a | foam | 484 | X |
| 132 | Me | 4-biphenyl | Z | 147-149° | 514 | X |
| 133 | Me | 4-biphenyl | E | foam | 514 | X |
| 134 | Me | 1-naphthyl | E/Z ^b | foam | 488 | X |
| 135 | Me | 2-naphthyl | Z | 171-172.5° | 488 | X |
| 136 | Me | 2-naphthyl | E | 123-125.5° | 488 | X |
| 137 | Me | 2-methoxyphenyl | E/Z ^c | foam | 468 | X |
| 138 | Me | 4-methoxyphenyl | E | foam | 468 | X |
| 139 | Me | 4-methoxyphenyl | Z | 104-107° | 468 | X |
| 140 | Me | 2-thienyl | E | foam | 444 | X |
| 141 | Me | 2-thienyl | Z | 121.5-122.5° | 444 | X |

Table 7 (cont'd)

| Compound # | R ₃ | Aryl | E/Z Isomers | Melting Point | MS (m/e)M ⁺ | C, H, N |
|---------------|----------------|----------------------|------------------|------------------|---------------------------|----------------|
| 142 | Me | 6-methoxy-2-naphthyl | E | foam | 518 | X |
| 143 | Me | 6-methoxy-2-naphthyl | Z | 125-127° | 518 | X |
| 144 | Me | 2-furyl | E | foam | 428 | X |
| 145 | Me | 2-furyl | Z | foam | 428 | X ^e |
| 146 | OMe | 2,3-dimethoxy-phenyl | E/Z ^d | foam | 514 | X |

^aE:Z ratio of 5:1

^bE:Z ratio of 5:4

^cE:Z ratio of 1:1

^dE:Z ratio of 1:3

^e 1/2 hydrate

Example 29

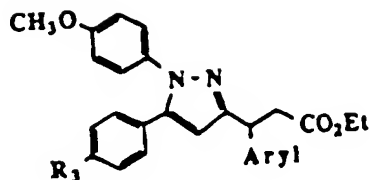
Ethyl 3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenyl propanoate (85)

Compound 81 (100 mg) was dissolved in EtOH (20 ml) and acetic acid (2 ml) and 10% palladium on carbon (50 mg) was added. The mixture was shaken on a Parr hydrogenator at 50 psi for 48 hr. The reaction mixture was filtered through celite and evaporated to give the title compound 85 as an oil, 100 mg. NMR (CDCl₃) δ 1.13 (3H, t, J = 7 Hz) 2.30 (3H, s), 3.0 (1H, d, J = 8 Hz; JAB = 24 Hz), 3.33 (1H, d, J = 8 Hz; JAB = 24 Hz), 3.79 (3H, s), 4.05 (2H, q, J = 7 Hz), 4.65 (1H, t, J = 8 Hz), 6.17 (1H, s), 6.82 (2H, d), 7.04 (4H, s), 7.06-7.50 (7H, m).

Following the above procedure, but substituting Compound 82 for 81 also affords compound 85.

Following the procedure of Example 29, but substituting the appropriate ester from Table 7 for compound 81 afforded the compounds of Table 8.

Table 8



| Compound # | Aryl | Melting Point | MS (m/e)M ⁺ | C.H.N |
|---------------|----------------|------------------|---------------------------|-------|
| 147 | 4-biphenylyl | foam | 516 | X |
| 148 | 4-methylphenyl | oil | 454 | X |
| 149 | 4-chlorophenyl | glass | 474 | X |
| 150 | 1-naphthyl | foam | 490 | X |

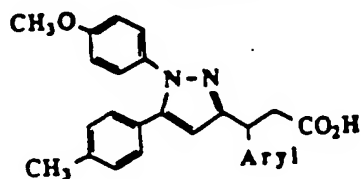
Example 30

3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenyl propanoic acid (86)

Following the procedure of Example 8, but substituting Compound 85 for 7 afforded the title compound 86, NMR (CDCl₃) δ 2.32 (3H, s), 2.8-3.7 (2H, ABX complex), 3.8 (3H, s), 4.64 (1H, t, J = 7 Hz), 6.18 (1H, s), 6.81 (2H, d), 7.04 (4H, s), 7.0-7.5 (7H, m).

Following the procedure of Example 8, but substituting the appropriate propanoate ester of Table 8 for compound 7 afforded the compounds of Table 9.

Table 9

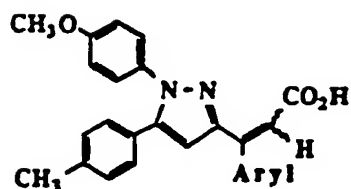


| Compound # | Aryl | Melting Point | MS (m/e)M ⁺ | C.H.N |
|---------------|----------------|------------------|---------------------------|-------|
| 151 | 4-fluorophenyl | 185-186° | 430 | X |
| 152 | 4-biphenylyl | 255-256° | 488 | X* |
| 153 | 4-chlorophenyl | 173-175° | 446 | X |
| 154 | 4-tolyl | 158-160° | 426 | X |

*1/2 hydrate

Following the procedure of Example 8, but substituting the appropriate propenoate esters of Table 7 for compound 7 afforded the compounds of Table 10.

Table 10



| Compound # | Aryl | E/Z Isomers | Melting Point | MS (m/e)M ⁺ | C.H.N |
|------------|----------------|-------------|---------------|------------------------|-------|
| 155 | phenyl | E | foam | 410 | X |
| 156 | 4-fluorophenyl | Z | 240-241° | 428 | X |
| 157 | 4-chlorophenyl | E | foam | 444 | X |
| 158 | 4-chlorophenyl | Z | 252-254° | 444 | X |
| 159 | 4-biphenyl | Z | 151-152° | 486 | X |
| 160 | 4-tolyl | Z | 150.5-153° | 424 | X |

Example 31

3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenyl-N-hydroxy-N-methylpropanamide (87)

Following the procedure of Example 9, but substituting Compound 86 for 18 afforded the title compound 87, NMR (CDCl₃) δ 2.31 (3H, s), 3.18 (3H, s), 2.8-3.7 (2H, ABX complex), 3.81 (3H, s), 4.64 (1H, t, J = 7 Hz), 6.19 (1H, s), 6.82 (2H, d), 7.04 (4H, s), 7.04-7.5 (7H, m).

Example 32

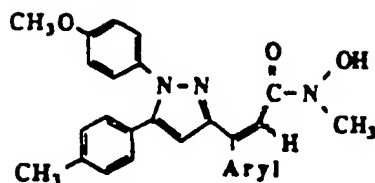
3-Biphenyl-N-hydroxy-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-N-methylpropanamide hemihydrate (161)

Following the procedure of Example 9, but substituting Compound 152 for 18 afforded the title compound 161 as a tan solid, mp = 155.5-157.5°; MS (m/e) 517(M⁺).

| | | | |
|---|-----------|----------|----------|
| Anal. Calcd. for C ₃₃ H ₃₁ N ₃ O ₃ ·1½H ₂ O: | | | |
| | C, 75.26; | H, 6.12; | N, 7.98 |
| Found: | C, 75.23; | H, 6.10; | N, 7.92. |

In addition, following the procedure of Example 9, but substituting the appropriate propenoic acid from Table 10 for 18 afforded the compounds of Table 11.

Table 11



| Compound # | Aryl | E/Z Isomers | Melting Point | MS (m/e)M ⁺ | C,H,N |
|---------------|----------------|----------------|------------------|---------------------------|----------------|
| 162 | phenyl | E | 137-139° | 439 | X |
| 163 | 4-fluorophenyl | E | foam | 457 | X ¹ |
| 164 | 4-chlorophenyl | E | foam | 473 | X |
| 165 | 4-chlorophenyl | Z | 111-115° | 473 | X ² |
| 166 | 4-biphenyl | Z | 167-169° | 515 | X |

Table 11 (con't)

| Compound # | Aryl | E/Z Isomers | Melting Point | MS (m/e)M ⁺ | C,H,N |
|---------------|----------------|----------------|------------------|---------------------------|----------------|
| 167 | 4-fluorophenyl | Z | foam | 457 | X ¹ |
| 168 | 4-biphenyl | E | 209-210° | 515 | X |

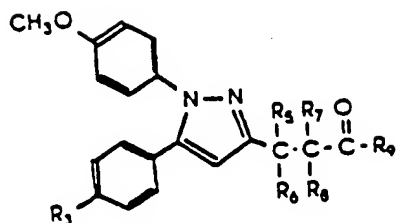
¹ 1/4 hydrate² 1/2 hydrate

IN VIVO ALLEVIATION OF INFLAMMATION

Polyarthritis was induced in Lewis strain laboratory rats (weight = about 200 grams) by injection of a suspension of *Mycobacterium butyricum* in mineral oil into the subplantar tissue of the mammal's hind paws. On day 10 after the injection, the rats were assigned to groups, and paw volumes and body weights were recorded. Paw volumes of the contralateral, uninjected hind paw were determined by mercury plethysmography. Per oral (p.o.) dosing began and continued for five consecutive days thereafter. On day 14 after the initial injection, approximately four hours after the final dose was administered, paw volumes and body weights were recorded and quantitated.

Anti-inflammatory activity of the N-hydroxypropanamide pyrazole compounds is expressed as the percent inhibition of paw volume increase. The results of this study for several compounds of the structure shown below are shown in Table 12, hereinafter.

Table 12



| %INH. | | | | | | | | %INH. p.o. |
|------------------|----|----|----|------------------|----|---------|----------|------------|
| No. | R3 | R5 | R6 | R7 | R8 | R9 | (mpk) | |
| 8 | Cl | H | H | Phenyl | H | OEt | 61% @ 10 | |
| 18 | Cl | H | H | 4-Chlorophenyl | H | CH | 39% @ 10 | |
| 23 | Me | H | H | 2-Methoxyphenyl | H | OH | 23% @ 25 | |
| 26 | Cl | H | H | 4-Chlorophenyl | H | N(OH)Me | 13% @ 10 | |
| 42 | Cl | H | H | spirocycloheptyl | - | N(OH)Me | 17% @ 10 | |
| 47 | Cl | H | H | Me | Me | N(OH)Me | 17% @ 10 | |
| 51 | Cl | Me | H | H | H | N(OH)Me | 40% @ 8 | |
| 52 | Cl | H | H | Me | H | N(OH)Me | 45% @ 15 | |
| 62 | Cl | - | - | Phenyl | - | N(OH)Me | 37% @ 15 | |
| 63 | Cl | - | - | cis-Cyclohexyl | - | N(OH)Me | 29% @ 10 | |
| 151 | Me | * | H | H | H | OH | 48% @ 10 | |
| 161 | Me | ** | H | H | H | N(OH)Me | 10% @ 10 | |
| * 4-Fluorophenyl | | | | | | | | |
| ** 4-Biphenyl | | | | | | | | |

STRUCTURE II (X=OMe)

| | | | | | | | |
|----|----|---|---|---|---|---------|----------|
| 75 | Cl | H | H | H | H | N(OH)Me | 20% @ 15 |
|----|----|---|---|---|---|---------|----------|

The following pyrazoles are described in the invention and the percent inhibition of paw volume increase for each is shown below.

| No. | %INH., p.o. (mpk) |
|-----|-------------------|
| 92 | 27% @ 10 |
| 94 | 29% @ 10 |
| 105 | 49% @ 15 |
| 108 | 25% @ 10 |
| 155 | 62% @ 10 |
| 157 | 24% @ 10 |
| 164 | 22% @ 10 |

II. EX VIVO ARACHIDONIC ACID METABOLISM OF RAT PLEURAL EXUDATE CELLS

This assay determines the ability of orally administered compounds to inhibit arachidonic acid metabolism with rat pleural exudate cells, via the lipoxygenase and/or cyclooxygenase enzymes. Sprague-Dawley rats (250 - 275 gm) are fasted overnight. The next morning, an acute inflammatory response is induced by the intra-thoracic injection of 1 ml of 0.25% carrageenan. Three hours later the rats are dosed orally with the test compounds at a screening dose of 16.5-30 mpk. Thirty minutes to one hour later the rats are sacrificed and pleural fluid harvested. The exudate fluids are diluted 1:5 using Hanks BSS and stimulated using 10 µg/ml calcium ionophore A-23187. The reaction is stopped after 15 minutes by the addition of 25 µl of 1N HCl, and the samples are centrifuged at 1000 g to sediment the cells. The supernate is extracted and applied to a C-18 HPLC column. The arachidonic acid metabolites 12-HHT (cyclooxygenase), 5-HETE, and leukotriene B₄ (lipoxygenase) are eluted using an acetonitrile methanol gradient and detected by UV absorption at 235 and 270 nm.

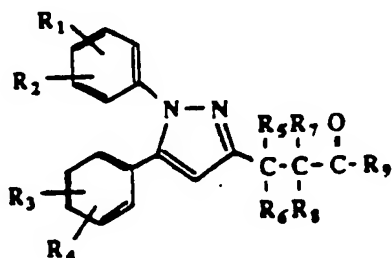
The percent inhibition of the arachidonic acid metabolites is indicative of the anti-inflammatory activity of the tested compound and the results of this method for several compounds of the invention are listed in Table 13. The values shown are the percent inhibition at the dose indicated except for the those cases in which the IC₅₀ value is given.

Table 13

| No. | %INH., p.o. Lipoxygenase (mpk) | %INH., p.o. Cyclooxygenase (mpk) |
|-----|--------------------------------|----------------------------------|
| 109 | 62% @ 30 | 94% @ 30 |
| 132 | 34% @ 16.5 | 54% @ 16.5 |
| 125 | IC ₅₀ = 9 mpk | IC ₅₀ = 14 mpk |
| 150 | 42% @ 30 | 6% @ 30 |
| 158 | 53% @ 17.5 | 32% @ 17.5 |
| 163 | IC ₅₀ = 10 mpk | IC ₅₀ = 1 mpk |
| 165 | 12% @ 30 | 55% @ 30 |
| 168 | 3% @ 30 | 39% @ 30 |

Claims

1. A compound of the formula

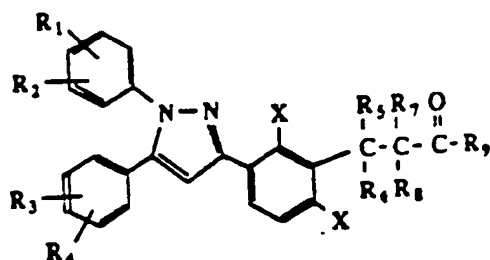


wherein

- (A) R₁, R₂, R₃ and R₄ are the same or different and are hydrogen, C₁ to C₆ alkyl, C₁ to C₆ alkoxy, amino, acetamido, phenyl, halo, hydroxy, C₁ to C₆ alkylsulfonyl, C₁ to C₆ alkylthio, nitro, trifluoromethyl, ω-trifluoromethyl C₁ to C₆ alkoxy; or
 R₁ and R₂, or R₃ and R₄, taken together with the phenyl group to which they are attached, form a naphthyl or substituted naphthyl group;
 (B) R₉ is hydroxy, -OR₁₀ or -N(OH)R₁₀ wherein R₁₀ is C₁ to C₆ alkyl; and
 (C) R₅, R₆, R₇ and R₈ are the same or different and are:
 hydrogen or C₁ to C₆ alkyl; or
 R₅ and R₆, or R₇ and R₈, when taken together are part of a spirocycloalkyl ring having 5-7 carbon atoms; or R₅, R₆, R₇ and R₈ when taken together are part of an aryl or a heterocyclic ring; or

R_6 and R_8 when taken together are part of a cyclohexyl, cyclohexenyl or 7-oxobicyclo[2.2.1]heptenyl ring; or R_5 , R_6 and R_7 are hydrogen and R_8 is phenyl, substituted phenyl (wherein the substituent is C_1 to C_6 alkoxy, di C_1 to C_6 alkoxy, carboxymethyl or carboxy), biphenyl, naphthyl or 4-chlorophenyl, provided that when R_8 is 4-chlorophenyl R_1 is 4-methoxy, R_2 is H, R_3 is 4-chloro, R_4 is H and R_9 is hydroxy, ethoxy or $N(OH)CH_3$; or R_5 , R_7 are R_8 are hydrogen and R_6 is phenyl, substituted phenyl (wherein the substituent is halo, C_1 to C_6 alkyl or C_1 to C_6 alkoxy), biphenyl, naphthyl or heterocycloaryl, provided that at least one of R_5 , R_6 , R_7 and R_8 is other than H, and the pharmaceutically acceptable salts thereof.

2. A compound of the formula



wherein R_1 , R_2 , R_3 and R_4 are as defined in claim 1, X is C_1 to C_6 alkoxy, R_5 , R_6 , R_7 and R_8 are hydrogen and R_9 is selected from hydroxy, $-OR_{10}$ wherein R_{10} is C_1 to C_6 alkyl and $N(OH)CH_3$.

3. A compound of claim 1 or claim 2 wherein R_1 and R_3 are selected from of halo C_1 to C_6 alkyl and C_1 to C_6 alkoxy; and R_2 and R_4 are hydrogen.

4. A compound of claim 1 which is ethyl 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-phenylpropanoate ;

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-(4-chlorophenyl)-N-hydroxy-N-methylpropanamide ;

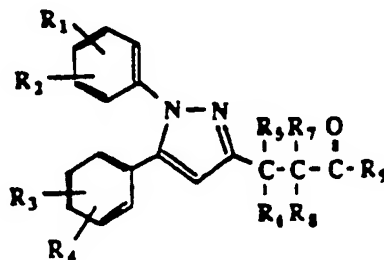
3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-2-spirocycloheptyl-N-methylpropanamide.

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2,N-dimethyl-N-hydroxypropanamide.

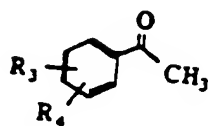
2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)pyrazolyl-3-yl]-N-hydroxy-N-methylbenzamide hemihydrate .

cis-2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-1-(N-hydroxy-N-methyl)-carboxamido-cyclohexane ; (E) -3-(4-fluorophenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl] propanoic acid ;

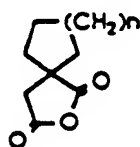
5. The process for the preparation of a compound of claim 1 of the formula



which comprises reaching a compound of the formula

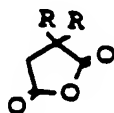


with (1) a cycloalkyl-1-carboxy-1-acetic acid anhydride of the formula

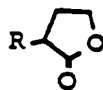


where R_5 and R_7 are hydrogen and R_6 and R_8 are part of a cyclohexyl, cyclohexenyl or 7-oxabicyclo-[2.2.1]heptenyl ring;

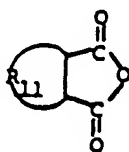
or (2) with a dialkyl-1-carboxy-1-acetic acid anhydride of the formula



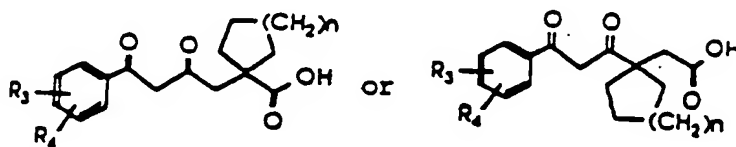
where R_5 , R_6 or R_7 , R_8 are each C_1 to C_6 alkyl;
or (3) with a butyrolactone of the formula



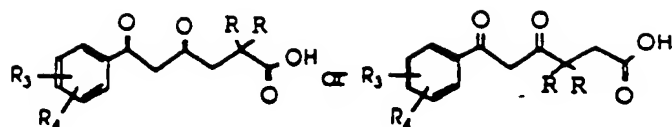
or a 4- C_1 to C_6 alkyl succinic anhydride;
where R_5 or R_7 is C_1 to C_6 alkyl;
or (4) with a bicyclic anhydride of the formula



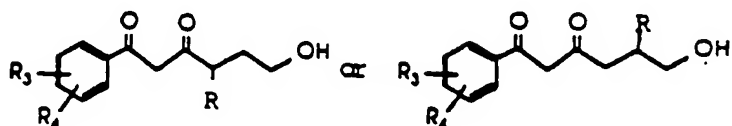
where R_5 , R_7 or R_6 , R_8 are phenyl or pyridyl to form (5) a mixture of spiroalkyl diketohexanoic acids of the formula



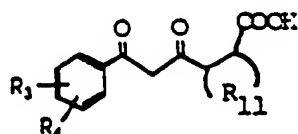
or (6) a mixture of 2- and 3- di C_1 to C_6 alkyl diketohexanoic acids of the formula



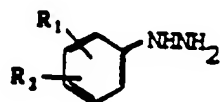
or (7) an aryl-1,3-dioxohexanol of the formula



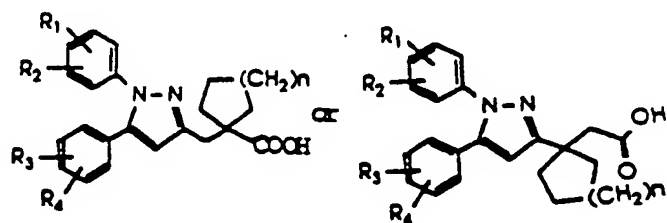
or (8) a propionic acid of the formula



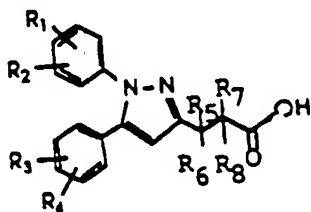
reacting the acid or dioxohexanol formed with a phenyl hydrazine of the formula



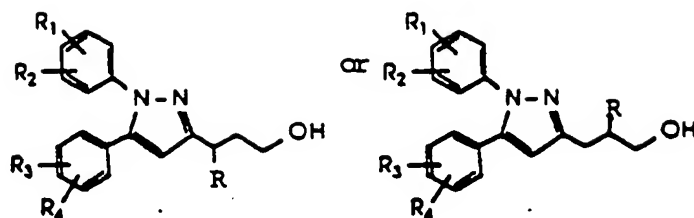
to form a (9) 2-cycloalkylsubstituted pyrazole propionic acid of the formula



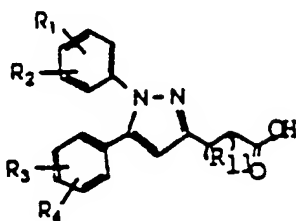
or a (10) 2- or 3-di C₁ to C₆ alkyl substituted pyrazole propionic acid of the formula



or (11) a pyrazole alcohol of the formula



or (12) a pyrazole propionic acid of the formula



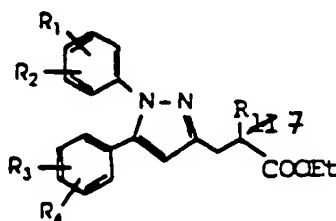
and (13) where R_9 is carboxyl, reacting the pyrazole alcohol with an oxidizing agent preferably a Jones reagent and where R_9 is OR_{10} reacting the pyrazole propionic acid with an esterifying agent, preferably diazomethane;

and (14) where R_9 is $-N(OH)R_{10}$ reacting each of the substituted pyrazole propionic acids formed with oxalyl chloride and reacting the acyl chloride formed with a N-lower alkylhydroxylamine;

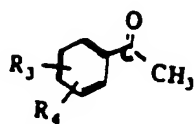
wherein R_1 , R_2 , R_3 and R_4 are selected from hydrogen, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, amino, acetamido, phenyl, halo, hydroxy, C_1 to C_6 alkylsulfonyl, C_1 to C_6 alkylthio, nitro, trifluoromethyl, ω -trifluoromethyl C_1 to C_6 alkoxy, or where R_1 , R_2 or R_3 , R_4 taken together with the phenyl group are naphthyl or substituted naphthyl; R is C_1 to C_6 alkyl; n is 1-3; R_{10} is C_1 to C_6 alkyl; R_{11} is phenyl or pyridyl; provided that at least one of R_5 , R_6 , R_7 and R_8 is other than hydrogen, and R_9 is as defined in claim 1.

6. The process of claim 5 wherein the compound is selected from ethyl 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-phenylpropanoate; 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-(4-chlorophenyl)-N-hydroxy-N-methylpropanamide; 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-2-spirocycloheptyl-N-methylpropanamide; 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2,N-dimethyl-N-hydroxypropanamide; 2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)pyrazolyl-3-yl]-N-hydroxy-N-methylbenzamide hemihydrate; cis-2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-1-(N-hydroxy-N-methyl)-carboxamido-cyclohexane; 3-[3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)pyrazol-3-yl]-2,6-dimethoxyphenyl]-N-hydroxy-N-methylpropanamide.

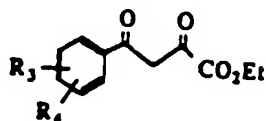
7. The process for the preparation of a compound of claim 1 of the formula



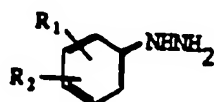
which comprises reacting an acetophenone of the formula



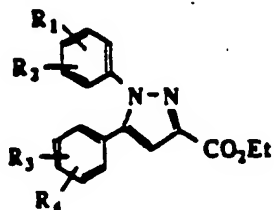
with diethyl oxalate to form a dioxobutanoate of the formula



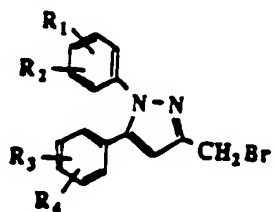
reacting the dioxobutanoate with a phenylhydrazine of the formula



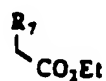
to form a carboethoxypyrazole of the formula



reducing the carboethoxypyrazole with a reducing agent, preferably lithium aluminium hydride, to form the corresponding hydroxymethyl analog, reacting the hydroxymethyl analog with phosphorus tribromide to form a bromomethylpyrazole of the formula

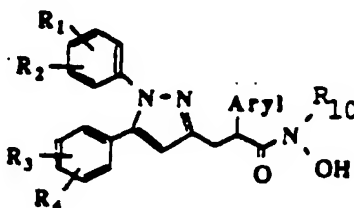


reacting the bromomethylpyrazole with an appropriately substituted aryl acetate of the formula

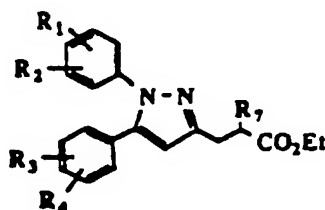


wherein R_1 , R_2 , R_3 and R_4 are the same or different and are selected from hydrogen, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, amino, acetamido, phenyl, halo, hydroxy, C_1 to C_6 alkylsulfonyl, C_1 to C_6 alkylthio, nitro, trifluoromethyl, ω -trifluoromethyl C_1 to C_6 alkoxy, or where R_1 , R_2 or R_3 , R_4 taken together with the phenyl group are naphthyl or substituted naphthyl; and R_7 is aryl.

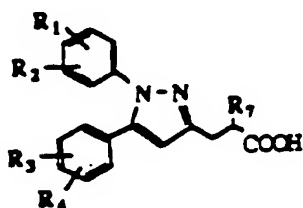
8. The process for the preparation of a compound of claim 1 of the formula



which comprises reacting a compound of the formula



with a base, preferably sodium hydroxide, to form a pyrazole propionic acid of the formula

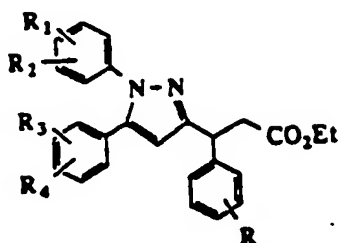


reacting the acid with oxalyl chloride to form the corresponding acyl chloride and reacting the acyl chloride with an N-alkylhydroxylamine of the formula

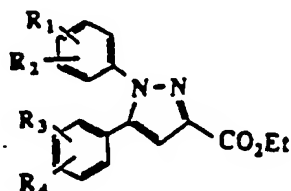


wherein R_1 , R_2 , R_3 and R_4 are the same or different and are selected from hydrogen, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, amino, acetamido, phenyl, halo, hydroxy, C_1 to C_6 alkylsulfonyl, C_1 to C_6 alkylthio, nitro, trifluoromethyl, ω -trifluoromethyl C_1 to C_6 alkoxy, or wherein R_1 , R_2 or R_3 , R_4 taken together with the phenyl group are naphthyl or substituted naphthyl; and R_7 is aryl and R_{10} is C_1 to C_6 alkyl.

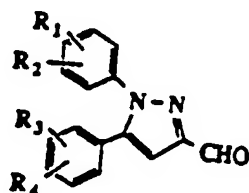
9. The process for the preparation of a compound of claim 1 of the formula



which comprises reacting a compound of the formula



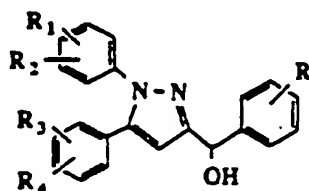
reducing the carboethoxypyrazole with a reducing agent, preferably hydrogen in the presence of a catalyst, to form the corresponding hydroxymethyl analog and reacting the hydroxymethyl analog with an oxidizing agent, preferably chromium trioxide, to form an aldehyde of the formula



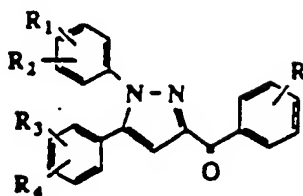
treating the aldehyde with a Grignard reagent of the formula



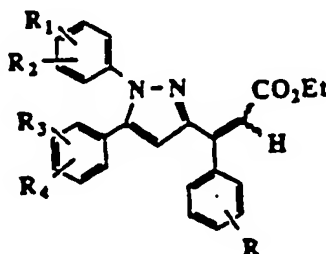
to form an alcohol of the formula



reacting the alcohol with a second oxidizing agent, preferably pyridinium chlorochromate, to form a ketone of the formula

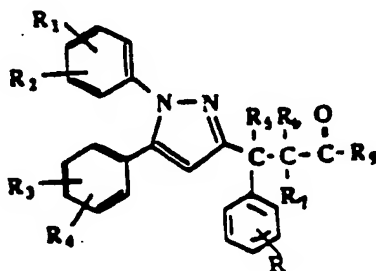


reacting the ketone with triethyl phosphonoacetate to form a pyrazole cinnamate of the formula

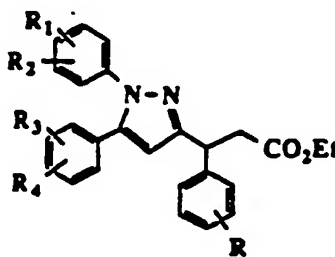


and reacting the cinnamate with a reducing agent, preferably hydrogen in the presence of a catalyst, wherein R_1 , R_2 , R_3 , and R_4 are the same or different and are selected from hydrogen, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, amino, acetamido, phenyl, halo, hydroxy, C_1 to C_6 alkylsulfonyl, C_1 to C_6 alkylthio, nitro, trifluoromethyl, ω -trifluoromethyl C_1 to C_6 alkoxy, or where R_1 , R_2 or R_3 , R_4 taken together with the phenyl group form a naphthyl or substituted naphthyl group; and R is halo, C_1 to C_6 alkyl, C_1 to C_6 alkoxy or phenyl.

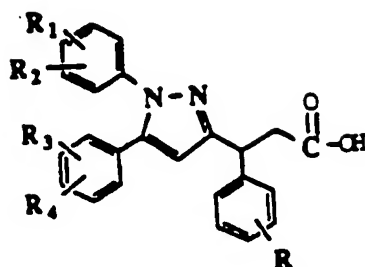
10. The process for preparing a compound of claim 1 of the formula



wherein R_1 , R_2 , R_3 and R_4 are as defined in claim 1, R_5 , R_6 and R_7 are hydrogen, R_9 is OH, OR_{10} or $N(OH)R_{10}$ and R is halo, C_1 to C_6 alkyl or C_1 to C_6 alkoxy which comprises reacting a carboethoxy pyrazole of the formula



(1) with a hydrolyzing agent, preferably sodium hydroxide, to form a pyrazole propionic acid of the formula

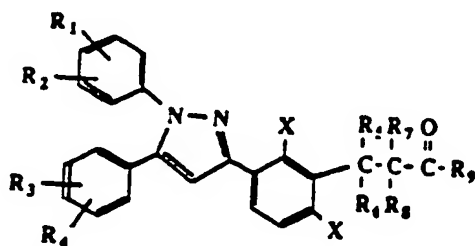


reacting the pyrazole propionic acid with oxalyl chloride and reacting the acyl chloride which forms with an N-alkylhydroxylamine of the formula

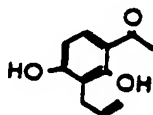


wherein R_{10} is C_1 to C_6 alkyl.

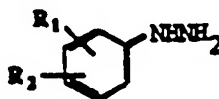
11. The process for preparing a compound of the formula



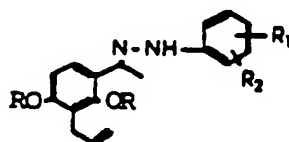
wherein R_1 - R_9 and X are as defined in claim 2, which comprises reacting a dihydroxy acetophenone of the formula



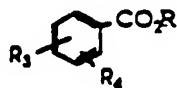
with an alkylating agent to form the corresponding 2,4-dialkoxy analog, reacting the dialkoxy analog with a phenylhydrazine of the formula



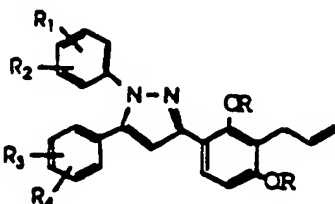
to form a hydrazone of the formula



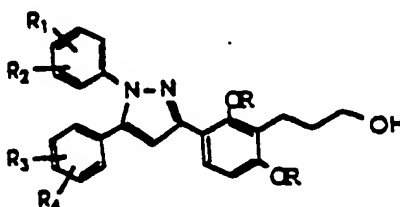
reacting the hydrazone with a base and then with a benzoate ester of the formula



to form a pyrazole of the formula



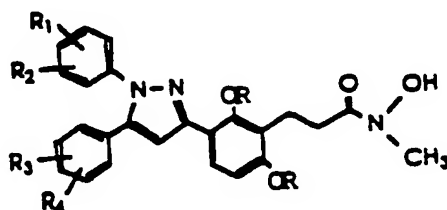
reacting the pyrazole with borane-methyl sulfide complex to form an alcohol of the formula



and where R_9 is OH, oxidizing the pyrazole alcohol with an oxidizing agent to form the corresponding pyrazole propionic acid;

and where R_9 is OR_{10} , reacting the pyrazole propionic acid with an esterifying agent;

and where R_9 is $N(OH)C_1$ to C_6 alkyl, reacting the pyrazole propionic acid with an acid chloride followed by reaction with an N-alkylhydroxylamine to form a compound of the formula



wherein R is C_1 to C_6 alkyl.

12. A compound of the formula



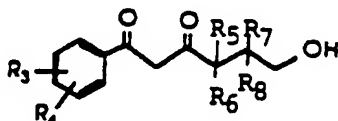
wherein R_3 and R_4 are as defined in claim 1 and R_7 and R_8 are hydrogen, cycloalkyl or C_1 to C_6 alkyl and alkali metal salts thereof, provided that when R_7 and R_8 are both hydrogen, R_3 and R_4 together are not hydrogen, 4-methyl, 3-methyl, 3,4-dimethyl, 2-methyl, 4-ethyl, 4-chloro, 4-fluoro or 3,4-dichloro.

- 5 13. A compound of claim 12 selected from 6-(4-chlorophenyl)-4,6-dioxo-2-spirocyclopentyl hexanoic acid; 6-(4-chlorophenyl)-4,6-dioxo-3-spirocyclopentyl hexanoic acid; 6-(4-chlorophenyl)-4,6-dioxo-2-spirocyclohexyl hexanoic acid; 6-(4-chlorophenyl)-4,6-dioxo-3-spirocyclohexyl hexanoic acid; 6-(4-chlorophenyl)-4,6-dioxo-2-spirocycloheptyl hexanoic acid; 6-(4-chlorophenyl)-4,6-dioxo-3-spirocycloheptyl hexanoic acid; and 6-(4-chlorophenyl)-2,2-dimethyl-4,6-dioxohexanoic acid.

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14. A compound of the formula

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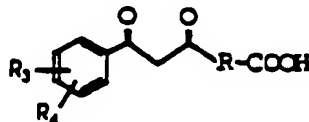
wherein R_3 and R_4 are as defined in claim 1 and at least one of R_5 , R_6 , R_7 and R_8 is C_1 to C_6 alkyl.

15. The compound of claim 14 which is selected from sodium 1-(4-chlorophenyl)-4-methyl-6-hydroxyhexane-1,3-dionate and 1-(4-chlorophenyl)-4-methyl-6-hydroxyhexane-1,3-dione.

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16. A compound of the formula

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wherein R_3 and R_4 are as defined in claim 1 and R is phenyl, substituted phenyl, pyridyl, substituted pyridyl, cyclohexyl, cyclohexenyl, or 7-oxobicyclo[2.2.1] heptenyl, but not including 4'-methoxy-2-carboxy dibenzoylmethane, 2-carboxy dibenzoylmethane, 3',4'-dichloro-2-carboxy dibenzoylmethane, or compounds wherein R is phenyl, R_3 is hydrogen or 3'-hydroxy and R_4 is 4'-hydroxy or 4'-alkoxy.

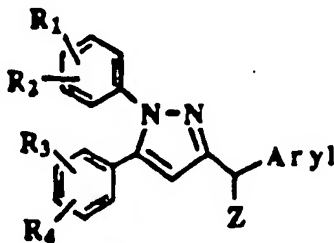
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17. The compound of claim 16 which is selected from 1-(4-chlorophenyl)-3-(2-carboxyphenyl)propane-1,3-dione; cis-1-[1-(4-chlorophenyl)-1,3-dioxoprop-3-yl]cyclohexane-2-carboxylic acid; trans-1-[1-(4-chlorophenyl)-1,3-dioxoprop-3-yl]cyclohexane-2-carboxylic acid; cis-1-[1-(4-chlorophenyl)-1,3-dioxoprop-3-yl]cyclohex-4-ene-2-carboxylic acid; 1-[3-(4-chlorophenyl)-1,3-dioxopropyl]-2-carboxycyclohex-1-ene; cis-1-[1-(4-chlorophenyl)-1,3-dioxoprop-3-yl]-6-carboxy-2,5-endoxo-3,4-cyclohexene; and 1-(4-chlorophenyl)-3-(6-carboxypyrid-2-yl)propan-1,3-dione.

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18. A compound of the formula

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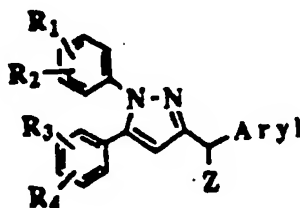


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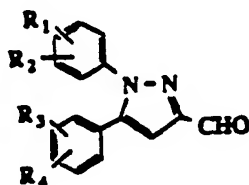
wherein Z is selected from OH, =O, =CHCO₂H, =CHCO₂R and =CHCON(OH)R, wherein R is C₁ to C₆ alkyl; R₁, R₂, R₃ and R₄ are the same or different and are selected from hydrogen, C₁ to C₆ alkyl, C₁ to C₆ alkoxy, amino, acetamido, phenyl, halo, hydroxy, C₁ to C₆ alkylsulfonyl, C₁ to C₆ alkylthio, nitro, trifluoromethyl, ω-trifluoromethyl C₁ to C₆ alkoxy, or R₁, R₂ or R₃, R₄ taken together with the phenyl group to which they are attached form a naphthyl or substituted naphthyl group; and aryl is selected from phenyl, halophenyl, mono- or di- C₁ to C₆ alkoxy phenyl, biphenyl, naphthyl, C₁ to C₆ alkoxy naphthyl, tolyl, thienyl and furyl.

19. A compound of claim 18 selected from 1-(4-methoxyphenyl)-3-(4-methylbenzoyl)-5-(4-methylphenyl)-pyrazole, (Z)-ethyl 3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-(4-methylphenyl)-propenoate, (E)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenyl-2-propenoic acid, (E)-3-(4-chlorophenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]propenoic acid, (Z)-3-(4-chlorophenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]propenoic acid, (E)-3-(4-fluorophenyl)-N-hydroxy-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-N-methylpropenamide, (E)-ethyl-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenyl-2-propenoate, (Z)-ethyl-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenyl-2-propenoate, (E)-ethyl-3-(4-fluorophenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-2-propenoate, and (Z)-ethyl-3-(4-fluorophenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenyl-2-propenoate.

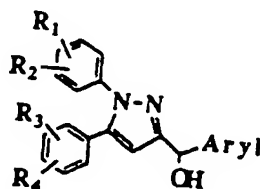
20. The process for the preparation of a compound of claim 18 or claim 19 of the formula



wherein Z is selected from OH, =O, =CHCO₂H, =CHCO₂R and =CHCON(OH)R, wherein R is C₁ to C₆ alkyl; R₁, R₂, R₃ and R₄ are the same or different and are selected from hydrogen, C₁ to C₆ alkyl, C₁ to C₆ alkoxy, amino, acetamido, phenyl, halo, hydroxy, C₁ to C₆ alkylsulfonyl, C₁ to C₆ alkylthio, nitro, trifluoromethyl, ω-trifluoromethyl C₁ to C₆ alkoxy, or R₁, R₂ or R₃, R₄ taken together with the phenyl group to which they are attached form a naphthyl or substituted naphthyl group; and aryl is selected from phenyl, halophenyl, mono- or di- C₁ to C₆ alkoxy phenyl, biphenyl, naphthyl, C₁ to C₆ alkoxy naphthyl, tolyl, thienyl and furyl, which comprises reacting a compound of the formula



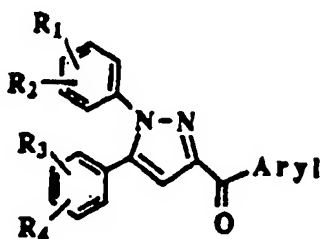
with a) an aryl magnesium halide; or b) an aryl halide; or c) an activated aryl derivative to form an alcohol of the formula



reacting the alcohol with an oxidizing agent to form a ketone of the formula

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reacting the ketone with a compound of the formula

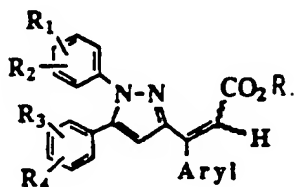
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to form an ester of the formula

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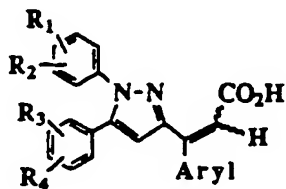
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hydrolyzing the ester to form an acid of the formula

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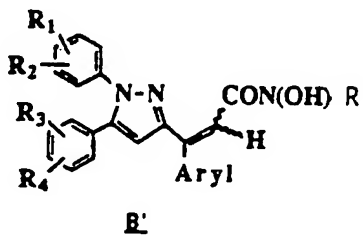


and reacting the acid with oxalyl chloride followed by reaction with an N-alkylhydroxylamine hydrochloride to form a hydroxamic acid of the formula

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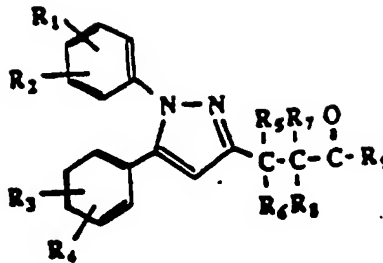
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Patentansprüche

1. Verbindung der Formel



worin

(A) R_1 , R_2 , R_3 und R_4 gleich oder verschieden sind und Wasserstoff, $C_1 - C_6$ -Alkyl, $C_1 - C_6$ -Alkoxy, Amino, Acetamido, Phenyl, Halogen, Hydroxy, $C_1 - C_6$ -Alkylsulfonyl, $C_1 - C_6$ -Alkylthio, Nitro, Trifluormethyl, ω -Trifluormethyl- $C_1 - C_6$ -Alkoxy sind; oder

R_1 und R_2 oder R_3 und R_4 mit der Phenylgruppe, an die sie gebunden sind, zusammen eine Naphthylgruppe oder eine substituierte Naphthylgruppe bilden;

(B) R_9 gleich Hydroxy, $-OR_{10}$ oder $-N(OH)R_{10}$ ist, wobei R_{10} für $C_1 - C_6$ -Alkyl steht; und

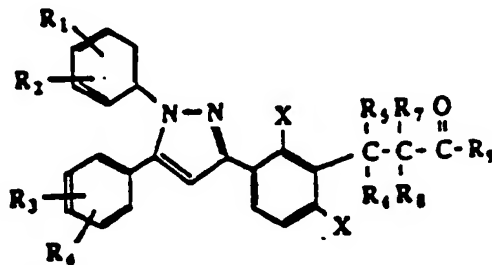
(C) R_5 , R_6 , R_7 und R_8 gleich oder verschieden sind und stehen für: Wasserstoff oder $C_1 - C_6$ -Alkyl; oder

R_5 und R_6 oder R_7 und R_8 zusammen Teil eines Spirocycloalkylringes mit 5 - 7 Kohlenstoffatomen sind; oder R_5 , R_6 , R_7 und R_8 zusammen Teil eines Aryl- oder eines heterocyclischen Ringes sind; oder

R_6 und R_8 zusammen Teil eines Cyclohexyl-, Cyclohexenyl- oder 7-Oxobicyclo[2.2.1]heptenylringes sind; oder R_5 , R_6 und R_7 sind Wasserstoff und R_8 ist Phenyl, substituiertes Phenyl (wobei der Substituent $C_1 - C_6$ -Alkoxy, di- $C_1 - C_6$ -Alkoxy, Carboxymethyl oder Carboxy ist), Biphenyl, Naphthyl oder 4-Chlorphenyl, mit der Maßgabe, daß, wenn R_8 gleich 4-Chlorphenyl ist, R_1 gleich 4-Methoxy ist, R_2 gleich H ist, R_3 gleich 4-Chlor ist, R_4 gleich H ist und R_9 gleich Hydroxy, Ethoxy oder $N(OH)CH_3$ ist; oder

R_5 , R_7 und R_8 sind Wasserstoff und R_6 ist Phenyl, substituiertes Phenyl (wobei der Substituent Halogen, $C_1 - C_6$ -Alkyl oder $C_1 - C_6$ -Alkoxy ist), Biphenyl, Naphthyl oder Heterocycloaryl, mit der Maßgabe, daß mindestens einer der Reste R_5 , R_6 , R_7 und R_8 nicht H ist, und die pharmazeutisch verträglichen Salze davon.

2. Verbindung der Formel



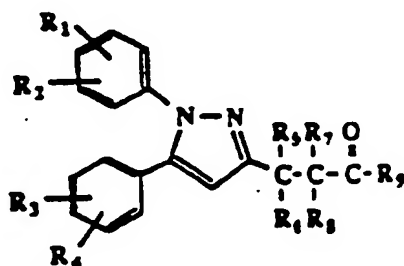
wobei R_1 , R_2 , R_3 und R_4 die in Anspruch 1 angegebene Bedeutung aufweisen, X gleich $C_1 - C_6$ -Alkoxy ist, R_5 , R_6 , R_7 und R_8 Wasserstoff sind und R_9 ausgewählt ist aus Hydroxy, $-OR_{10}$, wobei R_{10} eine $C_1 - C_6$ -Alkylgruppe und $N(OH)CH_3$ ist.

3. Verbindung nach Anspruch 1 oder Anspruch 2, wobei R_1 und R_3 ausgewählt sind aus Halogen, $C_1 - C_6$ -Alkyl und $C_1 - C_6$ -Alkoxy; und R_2 und R_4 Wasserstoff sind.

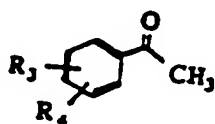
4. Verbindung nach Anspruch 1, die

Ethyl-3-[5-(4-chlorphenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-phenylpropanoat;
 3-[5-(4-Chlorphenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-(4-chlorphenyl)-N-hydroxy-N-methylpropanamid;
 3-[5-(4-Chlorphenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-2-spirocycloheptyl-N-methylpropanamid;
 3-[5-(4-Chlorphenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2,N-dimethyl-N-hydroxypropanamid;
 2-[5-(4-Chlorphenyl)-1-(4-methoxyphenyl)-pyrazolyl-3-yl]-N-hydroxy-N-methylbenzamid-Hemihydrat;
 cis-2-[5-(4-Chlorphenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-1-(N-hydroxy-N-methyl)-carboxamido-cyclohexan;
 (E)-3-(4-Fluorphenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-propansäure ist.

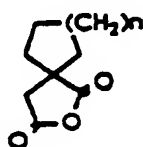
5. Verfahren zur Herstellung einer Verbindung nach Anspruch 1 gemäß der Formel



umfassend die Umsetzung einer Verbindung der Formel

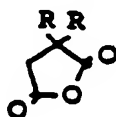


mit (1) einem Cycloalkyl-1-carboxy-1-essigsäureanhydrid der Formel



wobei R5 und R7 Wasserstoff sind und R6 und R8 Teil eines Cyclohexyl-, Cyclohexenyl- oder 7-Oxabicyclo[2.2.1]heptenylringes sind;

oder (2) mit einem Dialkyl-1-carboxy-1-essigsäureanhydrid der Formel

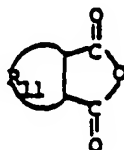


wobei R5, R6 oder R7, R8 jeweils C1 - C6-Alkyl sind;

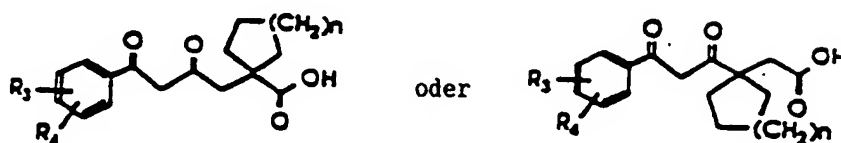
oder (3) mit einem Butyrolacton der Formel



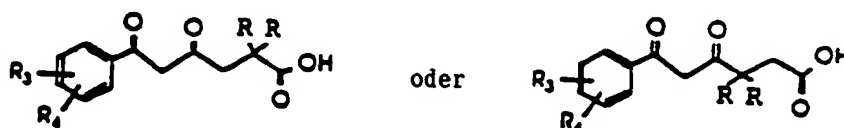
oder einem 4-C₁ - C₆-Alkylsuccinanhydrid;
wobei R₅ oder R₇ für C₁ - C₆-Alkyl steht;
oder (4) mit einem bicyclischen Anhydrid der Formel



wobei R₅, R₇ oder R₆, R₈ Phenyl oder Pyridyl sind, um (5) ein Gemisch zu bilden aus Spiroalkyl-
diketohexansäuren der Formeln



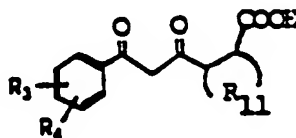
oder (6) ein Gemisch aus 2- und 3-Di-C₁ -C₆-Alkyldiketohexansäuren der Formeln



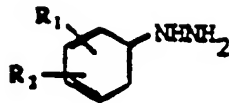
oder (7) ein Aryl-1,3-dioxohexanol der Formel



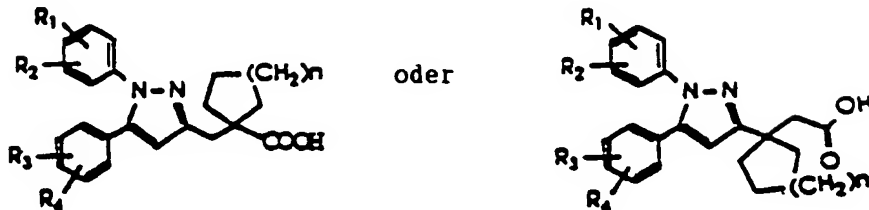
oder (8) eine Propionsäure der Formel



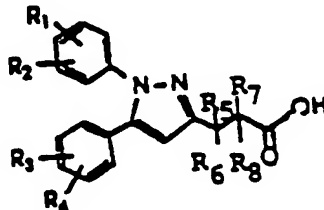
Umsetzen der gebildeten Säure oder des Dioxohexanols mit einem Phenylhydrazin der Formel



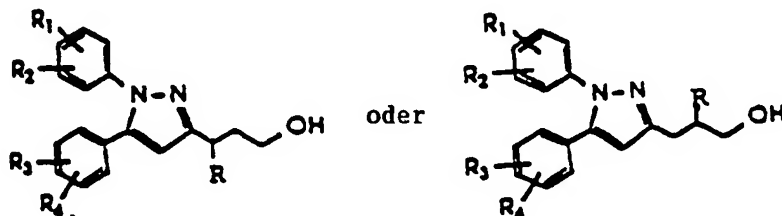
um eine (9) 2-cycloalkyl-substituierte Pyrazolpropionsäure der Formel



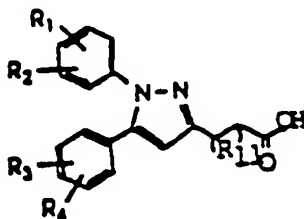
oder eine (10) 2- oder 3-Di- $\text{C}_1 - \text{C}_6$ -alkylsubstituierte Pyrazolpropionsäure der Formel



oder (11) einen Pyrazolalkohol der Formel



oder (12) eine Pyrazolpropionsäure der Formel



zu bilden, und (13), wenn R_9 eine Carboxygruppe ist, Umsetzen des Pyrazolalkohols mit einem Oxidationsmittel, vorzugsweise einem Jones-Reagens, und wenn R_9 gleich OR_{10} ist, Umsetzen der Pyrazolpropionsäure mit einem Veresterungsmittel, vorzugsweise Diazomethan;

und (14), wenn R_9 gleich $-\text{N}(\text{OH})\text{R}_{10}$ ist, Umsetzen einer jeden der gebildeten substituierten Pyrazolpropionsäuren mit Oxalylchlorid und Umsetzen des gebildeten Acylchlorids mit einem niedrigen

N-Alkylhydroxylamin;

wobei R_1 , R_2 , R_3 und R_4 ausgewählt sind aus Wasserstoff, C_1 - C_6 -Alkyl, C_1 - C_6 -Alkoxy, Amino, Acetamido, Phenyl, Halogen, Hydroxy, C_1 - C_6 -Alkylsulfonyl, C_1 - C_6 -Alkylthio, Nitro, Trifluormethyl, ω -Trifluormethyl- C_1 - C_6 -Alkoxy, oder, wobei R_1 , R_2 oder R_3 , R_4 zusammen mit der Phenylgruppe Naphthyl oder substituiertes Naphthyl sind; R gleich C_1 - C_6 -Alkyl ist; n gleich 1-3 ist; R_{10} gleich C_1 - C_6 -Alkyl ist; R_{11} gleich Phenyl oder Pyridyl ist; mit der Maßgabe, daß mindestens einer der Reste R_5 , R_6 , R_7 und R_8 nicht Wasserstoff ist, und R_9 die in Anspruch 1 angegebene Bedeutung aufweist.

6. Verfahren nach Anspruch 5, wobei die Verbindung ausgewählt ist aus

Ethyl-3-[5-(4-chlorphenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-phenylpropanoat;

3-[5-(4-Chlorphenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-(4-chlorphenyl)-N-hydroxy-N-methylpropanamid;

3-[5-(4-Chlorphenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-2-spirocycloheptyl-N-methylpropanamid;

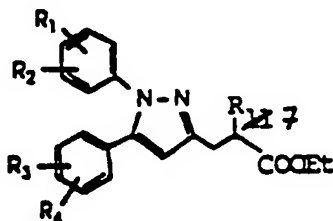
3-[5-(4-Chlorphenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2,N-dimethyl-N-hydroxypropanamid;

2-[5-(4-Chlorphenyl)-1-(4-methoxyphenyl)-pyrazolyl-3-yl]-N-hydroxy-N-methylbenzamid-Hemihydrat;

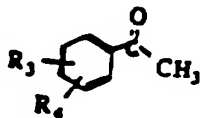
cis-2-[5-(4-Chlorphenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-1-(N-hydroxy-N-methyl)-carboxamid-cyclohexan;

3-[3-[5-(4-Chlorphenyl)-1-(4-methoxyphenyl)-pyrazol-3-yl]-2,6-dimethoxyphenyl]-N-hydroxy-N-methylpropanamid.

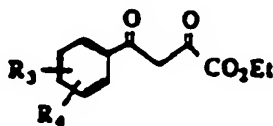
7. Verfahren zur Herstellung einer Verbindung nach Anspruch 1 gemäß der Formel



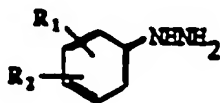
umfassend das Umsetzen eines Acetophenons der Formel



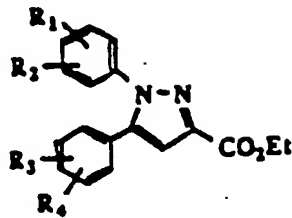
mit Diethyloxalat, um ein Dioxobutanoat der Formel



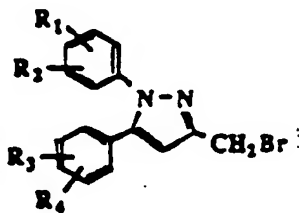
zu bilden, Umsetzen des Dioxobutanoats mit einem Phenylhydrazin der Formel



um ein Carboethoxypyrazol der Formel



zu bilden, Reduzieren des Carboethoxypyrazols mit einem Reduktionsmittel, vorzugsweise Lithiumaluminiumhydrid, um das entsprechende Hydroxymethylanalog zu bilden, Umsetzen des Hydroxymethylanalog mit Phosphortribromid, um ein Brommethylpyrazol der Formel

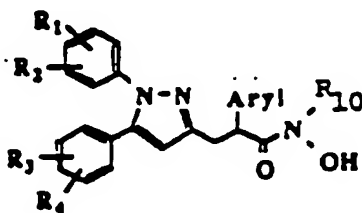


zu bilden, Umsetzen des Brommethylpyrazols mit einem geeignet substituierten Arylacetat der Formel

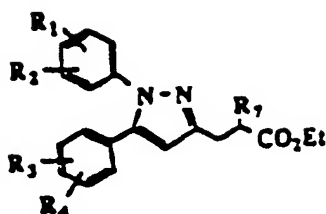


wobei R_1 , R_2 , R_3 und R_4 gleich oder verschieden sind und ausgewählt sind aus Wasserstoff, $C_1 - C_6$ -Alkyl, $C_1 - C_6$ -Alkoxy, Amino, Acetamido, Phenyl, Halogen, Hydroxy, $C_1 - C_6$ -Alkylsulfonyl, $C_1 - C_6$ -Alkylthio, Nitro, Trifluormethyl, ω -Trifluormethyl- $C_1 - C_6$ -Alkoxy, oder, wenn R_1 , R_2 oder R_3 , R_4 mit der Phenylgruppe zusammengekommen sind, Naphthyl oder substituiertes Naphthyl bilden; und R_7 Aryl ist.

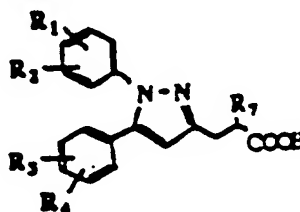
8. Verfahren zur Herstellung einer Verbindung nach Anspruch 1 gemäß der Formel



umfassend das Umsetzen einer Verbindung der Formel



mit einer Base, vorzugsweise Natriumhydroxid, um eine Pyrazolpropionsäure der Formel

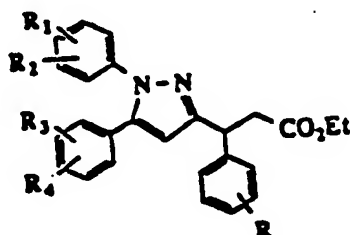


zu bilden, Umsetzen der Säure mit Oxalylchlorid, um das entsprechende Acylchlorid zu bilden, und Umsetzen des Acylchlorids mit einem N-Alkylhydroxylamin der Formel

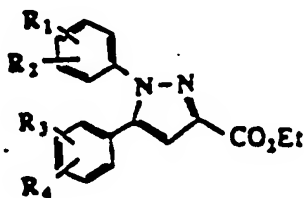


wobei R_1 , R_2 , R_3 und R_4 gleich oder verschieden sind und ausgewählt sind aus Wasserstoff, $C_1 - C_6$ -Alkyl, $C_1 - C_6$ -Alkoxy, Amino, Acetamido, Phenyl, Halogen, Hydroxy, $C_1 - C_6$ -Alkylsulfonyl, $C_1 - C_6$ -Alkylthio, Nitro, Trifluormethyl, ω -Trifluormethyl- $C_1 - C_6$ -Alkoxy, oder wobei R_1 , R_2 oder R_3 , R_4 mit der Phenylgruppe zusammen Naphthyl oder substituiertes Naphthyl sind; und R_7 Aryl ist und R_{10} gleich $C_1 - C_6$ -Alkyl ist.

9. Verfahren zur Herstellung einer Verbindung nach Anspruch 1 der Formel



umfassend das Umsetzen einer Verbindung der Formel

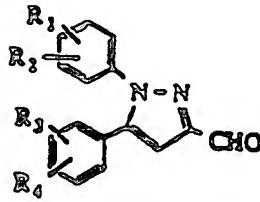


Reduzieren des Carboethoxypyrazols mit einem Reduktionsmittel, vorzugsweise Wasserstoff in Gegenwart eines Katalysators, um das entsprechende Hydroxymethylanalog zu bilden, und Umsetzen des

Hydroxymethylanalogs mit einem Oxidationsmittel, vorzugsweise Chromtrioxid, um einen Aldehyd der Formel

5

10



zu bilden, Umsetzen des Aldehyds mit einem Grignard-Reagens der Formel

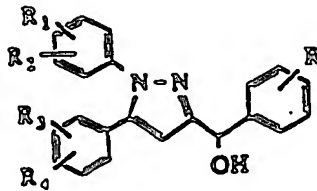
15



um einen Alkohol der Formel

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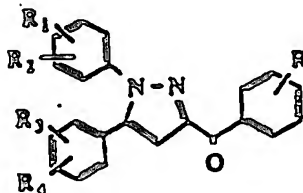


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zu bilden, Umsetzen des Alkohols mit einem zweiten Oxidationsmittel, vorzugsweise Pyridiniumchlorchromat, um ein Keton der Formel

35

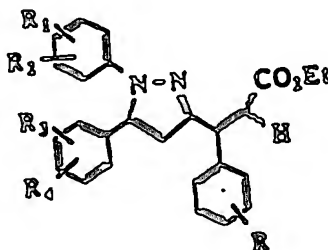
40



zu bilden, Umsetzen des Ketons mit Triethylphosphonoacetat, um ein Pyrazolcinnamat der Formel

45

50

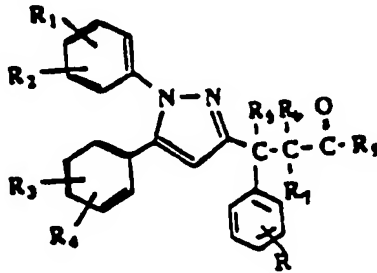


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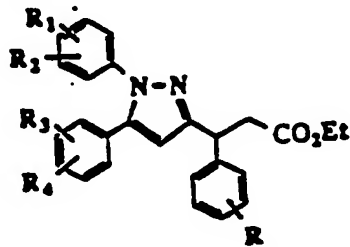
zu bilden, und Umsetzen des Cinnamats mit einem Reduktionsmittel, vorzugsweise Wasserstoff in Gegenwart eines Katalysators, wobei R₁, R₂, R₃ und R₄ gleich oder verschieden sind und ausgewählt sind aus Wasserstoff, C₁ - C₆-Alkyl, C₁ - C₆-Alkoxy, Amino, Acetamido, Phenyl, Halogen, Hydroxy, C₁ - C₆-Alkylsulfonyl, C₁ - C₆ - Alkylthio, Nitro, Trifluormethyl, ω-Trifluormethyl-C₁ - C₆-Alkoxy, oder wobei

R_1 , R_2 oder R_3 , R_4 mit der Phenylgruppe zusammen eine Naphthyl- oder eine substituierte Naphthylgruppe bilden; und R gleich Halogen, $C_1 - C_6$ -Alkyl, $C_1 - C_6$ -Alkoxy oder Phenyl ist.

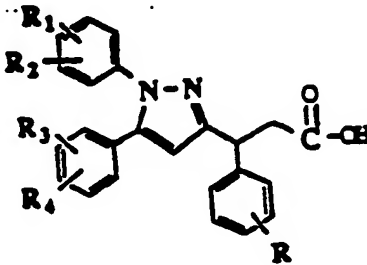
10. Verfahren zum Herstellen einer Verbindung nach Anspruch 1 der Formel



wobei R_1 , R_2 , R_3 und R_4 die in Anspruch 1 angegebene Bedeutung aufweisen, R_5 , R_6 und R_7 Wasserstoff sind, R_8 gleich OH, OR_{10} oder $N(OH)R_{10}$ ist und R gleich Halogen, $C_1 - C_6$ -Alkyl oder $C_1 - C_6$ -Alkoxy ist, umfassend das Umsetzen eines Carboethoxypyrazols der Formel



(1) mit einem Hydrolyisierungsmittel, vorzugsweise Natriumhydroxid, um eine Pyrazolpropionsäure der Formel

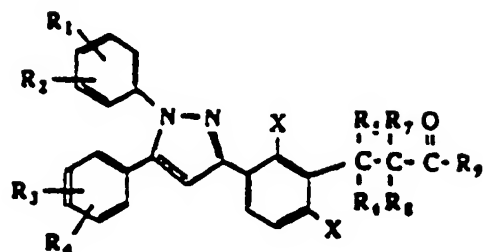


zu bilden, Umsetzen der Pyrazolpropionsäure mit Oxalylchlorid und Umsetzen des Acylchlorids, das sich bildet, mit einem N-Alkylhydroxylamin der Formel

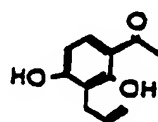
$R_{10}NHOH$,

wobei R_{10} gleich $C_1 - C_6$ -Alkyl ist.

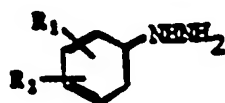
11. Verfahren zur Herstellung einer Verbindung der Formel



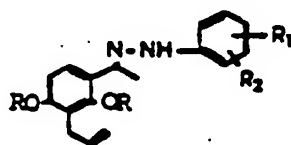
wobei $R_1 - R_9$ und X die in Anspruch 2 angegebene Bedeutung aufweisen, umfassend das Umsetzen eines Dihydroxyacetophenons der Formel



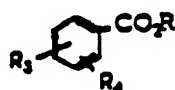
mit einem Alkylierungsmittel, um das entsprechende 2,4-Dialkoxyanalog zu bilden, Umsetzen des Dialkoxyanalog mit einem Phenylhydrazin der Formel



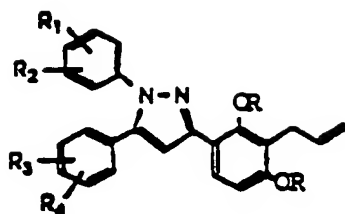
um ein Hydrazon der Formel



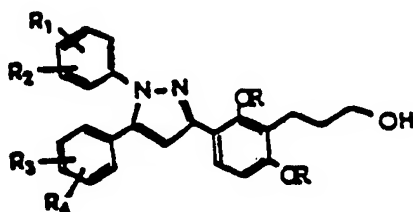
zu bilden, Umsetzen des Hydrazons mit einer Base und dann mit einem Benzoatester der Formel



um ein Pyrazol der Formel



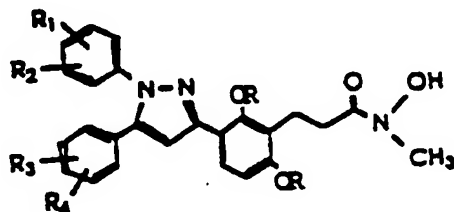
zu bilden, Umsetzen des Pyrazols mit Boranmethyldisulfidkomplex, um einen Alkohol der Formel



zu bilden, und wenn R_9 gleich OH ist, Oxidieren des Pyrazolalkohols mit einem Oxidationsmittel, um die entsprechende Pyrazolpropionsäure zu bilden;

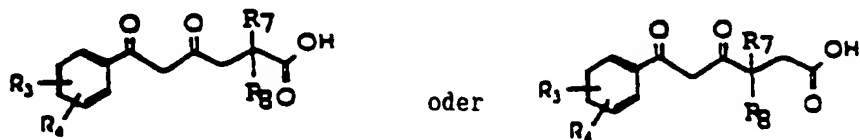
und wenn R_9 gleich OR_{10} ist, Umsetzen der Pyrazolpropionsäure mit einem Veresterungsmittel;

und wenn R_9 gleich $N(OH)-C_1 - C_6$ -Alkyl ist, Umsetzen der Pyrazolpropionsäure mit einem Säurechlorid, gefolgt von einer Umsetzung mit einem N-Alkylhydroxylamin, um eine Verbindung der Formel



zu bilden, wobei R gleich $C_1 - C_6$ -Alkyl ist.

12. Verbindung der Formel



wobei R_3 und R_4 die in Anspruch 1 angegebene Bedeutung aufweisen und R_7 und R_8 Wasserstoff, Cycloalkyl oder $C_1 - C_6$ -Alkyl und Alkalimetallsalze davon sind, mit der Maßgabe, daß, wenn R_7 und R_8 beide Wasserstoff sind, R_3 und R_4 zusammen nicht Wasserstoff, 4-Methyl, 3-Methyl, 3,4-Dimethyl, 2-Methyl, 4-Ethyl, 4-Chlor, 4-Fluor oder 3,4-Dichlor sind.

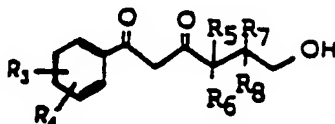
13. Verbindung nach Anspruch 12, ausgewählt aus

6-(4-Chlorphenyl)-4,6-dioxo-2-spirocyclopentylhexansäure;

6-(4-Chlorphenyl)-4,6-dioxo-3-spirocyclopentylhexansäure;

6-(4-Chlorphenyl)-4,6-dioxo-2-spirocyclohexylhexansäure;
 6-(4-Chlorphenyl)-4,6-dioxo-3-spirocyclohexylhexansäure;
 6-(4-Chlorphenyl)-4,6-dioxo-2-spirocycloheptylhexansäure;
 6-(4-Chlorphenyl)-4,6-dioxo-3-spirocycloheptylhexansäure; und
 6-(4-Chlorphenyl)-2,2-dimethyl-4,6-dioxohexansäure.

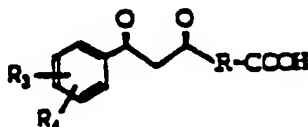
14. Verbindung der Formel



wobei R_3 und R_4 die in Anspruch 1 angegebene Bedeutung aufweisen und mindestens einer der Reste R_5 , R_6 , R_7 und R_8 eine C_1 - C_6 -Alkylgruppe ist.

15. Verbindung nach Anspruch 14, ausgewählt aus Natrium-1-(4-Chlorphenyl)-4-methyl-6-hydroxyhexan-1,3-dionat und 1-(4-Chlorphenyl)-4-methyl-6-hydroxyhexan-1,3-dion.

16. Verbindung der Formel



wobei R_3 und R_4 die in Anspruch 1 angegebene Bedeutung aufweisen und R gleich Phenyl, substituiertes Phenyl, Pyridyl, substituiertes Pyridyl, Cyclohexyl, Cyclohexenyl oder 7-Oxobicyclo-[2.2.1]heptenyl ist, wobei jedoch 4'-Methoxy-2-carboxy-dibenzoylmethan, 2-Carboxy-dibenzoylmethan, 3',4'-Dichlor-2-carboxy-dibenzoylmethan oder Verbindungen, in denen R gleich Phenyl ist, R_3 gleich Wasserstoff oder 3'-Hydroxy ist und R_4 gleich 4'-Hydroxy oder 4'-Alkoxy ist, nicht umfaßt sind.

17. Verbindung nach Anspruch 16, die ausgewählt ist aus 1-(4-Chlorphenyl)-3-(2-carboxyphenyl)propan-1,3-dion;

cis-1-[1-(4-Chlorphenyl)-1,3-dioxoprop-3-yl]cyclohexan-2-carbonsäure;

trans-1-[1-(4-Chlorphenyl)-1,3-dioxoprop-3-yl]cyclohexan-2-carbonsäure;

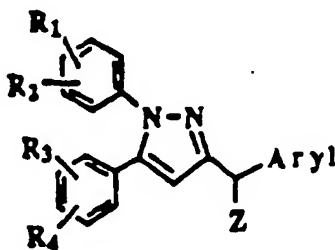
cis-1-[1-(4-Chlorphenyl)-1,3-dioxoprop-3-yl]cyclohex-4-en-2-carbonsäure;

1-[3-(4-Chlorphenyl)-1,3-dioxopropyl]-2-carboxycyclohex-1-en;

cis-1-[1-(4-Chlorphenyl)-1,3-dioxoprop-3-yl]-6-carboxy-2,5-endoxo-3,4-cyclohexen; und

1-(4-Chlorphenyl)-3-(6-carboxypyrid-2-yl)propan-1,3-dion.

18. Verbindung der Formel



worin Z ausgewählt ist aus OH, = O, =CHCO₂H, =CHCO₂R und =CHCON(OH)R, wobei R gleich C₁ - C₆-Alkyl ist; R₁, R₂, R₃ und R₄ gleich oder verschieden sind und ausgewählt sind aus Wasserstoff, C₁ - C₆-Alkyl, C₁ - C₆-Alkoxy, Amino, Acetamido, Phenyl, Halogen, Hydroxy, C₁ - C₆-Alkylsulfonyl, C₁ - C₆-Alkylthio, Nitro, Trifluormethyl, ω-Trifluormethyl-C₁ - C₆-Alkoxy oder R₁, R₂ oder R₃, R₄ mit der Phenylgruppe, an die sie gebunden sind, zusammen eine Naphthyl- oder eine substituierte Naphthylgruppe bilden; und Aryl ausgewählt ist aus Phenyl, halogeniertem Phenyl, Mono- oder Di-C₁ - C₆-Alkoxyphenyl, Biphenyl, Naphthyl, C₁ - C₆-Alkoxy-naphthyl, Toly, Thienyl und Furyl.

19. Verbindung nach Anspruch 18, ausgewählt aus 1-(4-Methoxyphenyl)-3-(4-methylbenzoyl)-5-(4-methylphenyl)pyrazol;

(Z)-Ethyl-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-(4-methylphenyl)propenoat,

(E)-3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenyl-2-propensäure,

(E)-3-(4-Chlorphenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]propensäure,

(Z)-3-(4-Chlorphenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]propensäure,

(E)-3-(4-Fluorphenyl)-N-hydroxy-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-N-methylpropenamid,

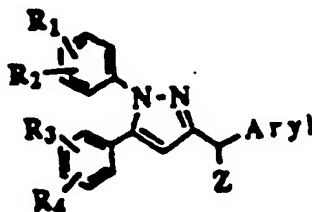
(E)-Ethyl-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenyl-2-propenoat,

(Z)-Ethyl-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenyl-2-propenoat,

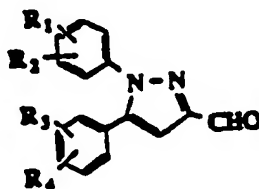
(E)-Ethyl-3-(4-Fluorphenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-2-propenoat und

(Z)-Ethyl-3-(4-fluorphenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenyl-2-propenoat.

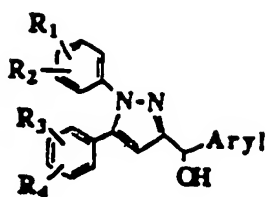
20. Verfahren zur Herstellung einer Verbindung nach Anspruch 18 oder Anspruch 19 gemäß der Formel



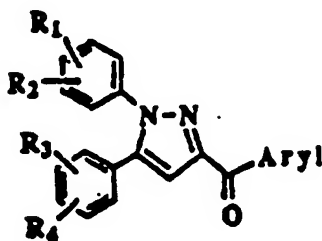
wobei Z ausgewählt ist aus OH, = O, =CHCO₂H, =CHCO₂R und =CHCON(OH)R, wobei R C₁ - C₆-Alkyl ist; R₁, R₂, R₃ und R₄ gleich oder verschieden sind und ausgewählt sind aus Wasserstoff, C₁ - C₆-Alkyl, C₁ - C₆-Alkoxy, Amino, Acetamido, Phenyl, Halogen, Hydroxy, C₁ - C₆-Alkylsulfonyl, C₁ - C₆-Alkylthio, Nitro, Trifluormethyl, ω-Trifluormethyl-C₁ - C₆-Alkoxy oder R₁, R₂ oder R₃, R₄ zusammen mit der Phenylgruppe, an die sie gebunden sind, eine Naphthyl- oder eine substituierte Naphthylgruppe bilden; und Aryl ausgewählt ist aus Phenyl, halogeniertem Phenyl, Mono- oder Di-C₁ - C₆-Alkoxyphenyl, Biphenyl, Naphthyl, C₁ - C₆-Alkoxy-naphthyl, Toly, Thienyl und Furyl, umfassend das Umsetzen einer Verbindung der Formel



mit a) einem Arylmagnesiumhalogenid; oder b) einem Arylhalogenid; oder c) einem aktivierten Arylderivat, um einen Alkohol der Formel



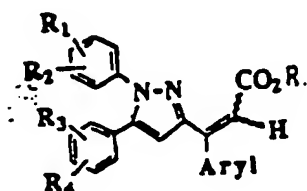
10 zu bilden, Umsetzen des Alkohols mit einem Oxidationsmittel, um ein Keton der Formel



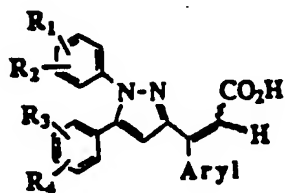
zu bilden, Umsetzen des Ketons mit einer Verbindung der Formel



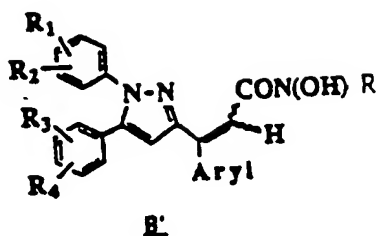
um einen Ester der Formel



zu bilden, Hydrolysieren des Esters, um eine Säure der Formel



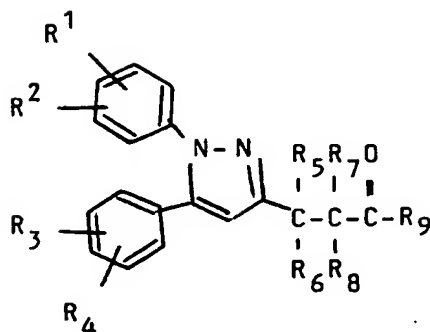
zu bilden, und Umsetzen der Säure mit Oxalylchlorid und anschließendes Umsetzen mit einem N-Alkylhydroxylamin-hydrochlorid, um eine Hydroxamsäure der Formel



zu bilden.

Revendications

1. Composé de la formule



où

(A) R₁, R₂, R₃ et R₄ sont identiques ou différents et sont hydrogène, alkyle C₁ à C₆, alcoxy C₁ à C₆, amino, acétamido, phényle, halo, hydroxy, alkyle (C₁ à C₆)sulfonyl, alkylthio C₁ à C₆, nitro, trifluorométhyle, ω-trifluorométhyle, alcoxy C₁ à C₆; ou

R₁ et R₂ ou bien R₃ et R₄ pris ensemble avec le groupe phényle auquel ils sont attachés, forment un groupe naphthyle ou naphthyle substitué;

(B) R₅ est hydroxy, -OR₁₀ ou -N(OH)R₁₀, où R₁₀ est alkyle C₁ à C₆; et

(C) R₅, R₆, R₇ et R₈ sont identiques ou différents et sont : hydrogène ou alkyle C₁ à C₆; ou

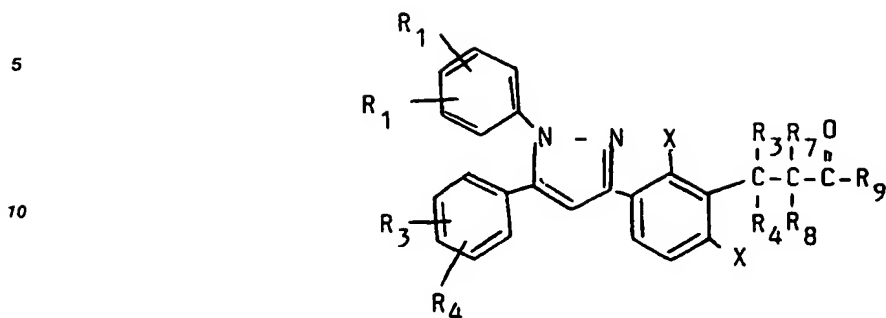
R₅ et R₆ ou bien R₇ et R₈, lorsqu'ils sont pris ensemble, font partie d'un noyau de spirocycloalkyle ayant 5-7 atomes de carbone; ou bien R₅, R₆, R₇ et R₈, lorsqu'ils sont pris ensemble, font partie d'un noyau aryle ou hétérocyclique; ou

R₆ et R₈, quand ils sont pris ensemble, font partie d'un noyau cyclohexyle, cyclohexényle ou 7-oxobicyclo[2.2.1] - heptényle; ou bien R₅, R₆ et R₇ sont hydrogène et R₈ est phényle, phényle substitué (où le substituant est alcoxy C₁ à C₆, dialcoxy C₁ à C₆, carboxyméthyle ou carboxy), biphényle, naphthyle ou 4-chlorophényle, à condition que quand R₈ est 4-chlorophényle, R₁ soit 4-méthoxy, R₂ soit H, R₃ soit 4-chloro, R₄ soit H et R₉ soit hydroxy, éthoxy ou N(OH)CH₃; ou

R₅, R₇ et R₈ sont hydrogène et R₆ est phényle, phényle substitué (où le substituant est halo, alkyle C₁ à C₆ ou alcoxy C₁ à C₆), biphényle, naphthyle ou hétérocycloaryle,

à condition qu'au moins l'un de R₅, R₆, R₇ et R₈ soit autre que H, et leurs sels acceptables en pharmacie.

2. Composé de la formule



15 où R_1 , R_2 , R_3 et R_4 sont tels que définis à la revendication 1, X est alcoxy C_1 à C_6 , R_5 , R_6 , R_7 et R_8 sont hydrogène et R_9 est choisi parmi hydroxy, $-OR_{10}$ où R_{10} est alkyle C_1 à C_6 et $N(OH)CH_3$.

20 3. Composé de la revendication 1 ou de la revendication 2, où R_1 et R_3 sont choisis parmi halo, alkyle C_1 à C_6 et alcoxy C_1 à C_6 ; et R_2 et R_4 sont hydrogène.

25 4. Composé de la revendication 1, qui est 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-2-phénylpropanoate d'éthyle.

3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-2-(4-chlorophényl)-N-hydroxy-N-méthylpropanamide;

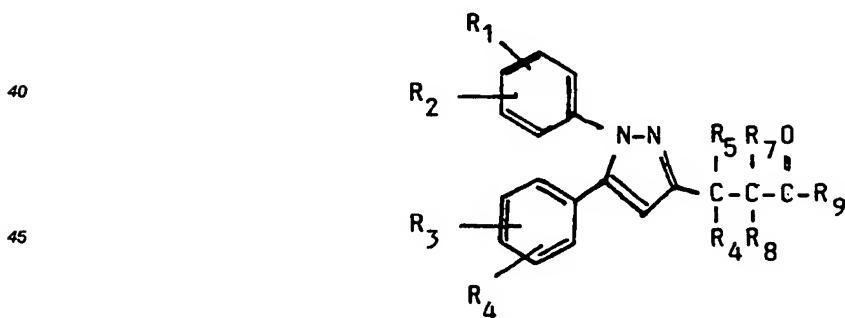
3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-hydroxy-2-spirocycloheptyl-N-méthylpropanamide.

3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-2,N-diméthyl-N-hydroxypropanamide.

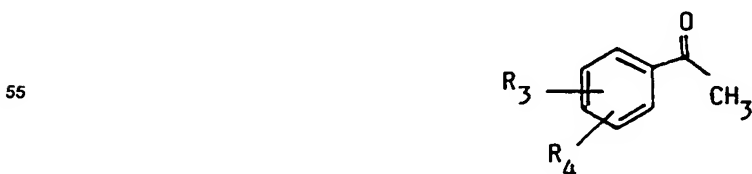
2-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-pyrazolyl-3-yl]-N-hydroxy-N-méthylbenzamide hémihydrate.

30 cis-2-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-1-(N-hydroxy-N-méthyl)-carboxamidocyclohexane; acide (E) -3-(4-fluorophényl)-3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]-propanoïque.

35 5. Procédé pour la préparation d'un composé de la revendication 1 de la formule

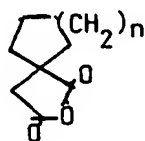


50 qui comprend la réaction d'un composé de la formule



avec (1) un anhydride d'acide cycloalkyl-1-carboxy-1-acétique de la formule

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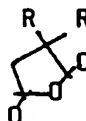


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où R_5 et R_7 sont hydrogène et R_6 et R_8 font partie d'un noyau cyclohexyle, cyclohexényle ou 7-oxabicyclo[2.2.1] heptényle;

ou bien (2) avec un anhydride d'acide dialkyl-1-carboxy-1-acétique de la formule

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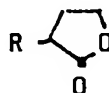


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où R_5 , R_6 ou R_7 , R_8 sont alkyle C_1 à C_6 ;

ou bien (3) avec une butyrolactone de la formule

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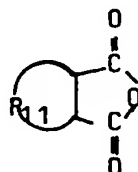
30

ou un anhydride 4-alkyle C_1 à C_6 succinique;

où R_5 ou R_7 est alkyle C_1 à C_6 ;

ou bien (4) avec un anhydride bicyclique de la formule

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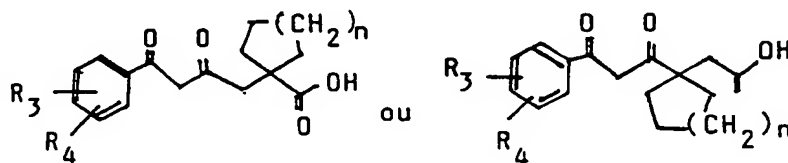


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où R_5 , R_7 ou bien R_6 , R_8 sont phényle ou pyridyle pour former (5) un mélange d'acides spiroalkyl dicétohexanoïques de la formule

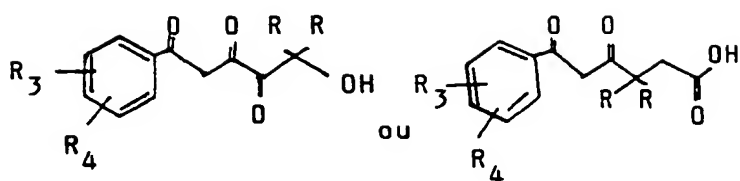
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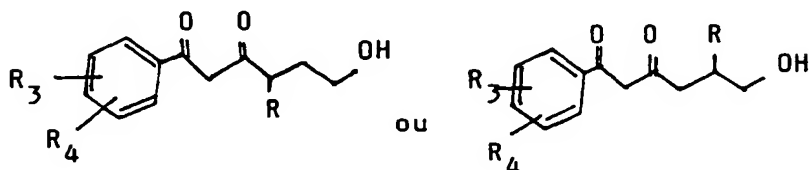


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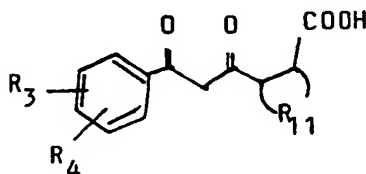
ou bien (6) un mélange d'acides 2- et 3-dialkyle C_1 à C_6 dicétohexanoïques de la formule



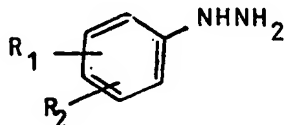
ou bien (7) un aryl-1,3-dioxohexanol de la formule



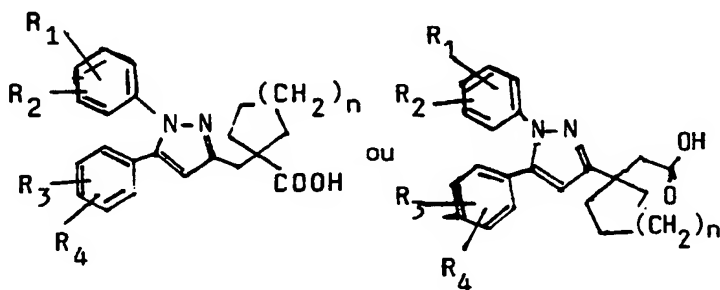
ou bien (8) un acide propionique de la formule



la réaction de l'acide ou du dioxohexanol formé avec une phényl hydrazine de la formule



pour former (9) un acide pyrazole propionique 2-cycloalkyle substitué de la formule :



ou bien (10) un acide pyrazole propionique 2- ou 3-dialkyle C1 à C6 substitué de la formule



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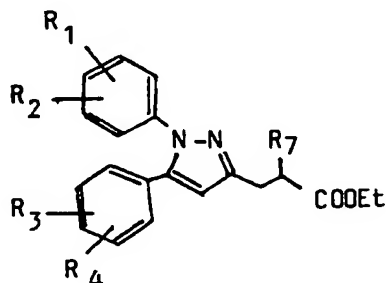
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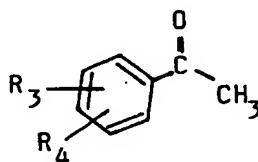
6. Procédé de la revendication 5, où le composé est choisi parmi 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-2-phénylpropanoate d'éthyle; 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-2-(4-chlorophényl)-N-hydroxy-N-méthylpropanamide; 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-hydroxy-2-spirocycloheptyl-N-méthylpropanamide; 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-2,N-diméthyl-N-hydroxypropanamide; 2-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-pyrazolyl]-3-yl]-N-hydroxy-N-méthylbenzamide hémihydrate; cis-2-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-pyrazolyl]-3-yl]-N-hydroxy-N-méthylpropanamide.

thoxyphényl)-3-pyrazolyl]-1-(N-hydroxy-N-méthyl)-carboxamido-cyclohexane; 3-[3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-pyrazol-3-yl]-2,6-diméthoxyphényl]-N-hydroxy-N-méthyl-propanamide.

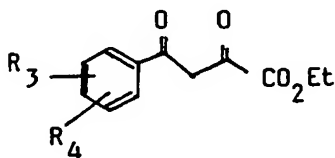
7. Procédé pour la préparation d'un composé de la revendication 1 de la formule



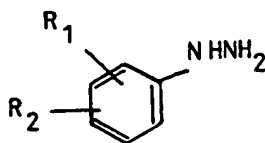
qui comprend la réaction d'une acétophénone de la formule



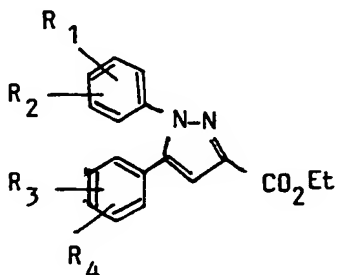
avec de l'oxalate de diéthyle pour former un dioxobutanoate de la formule



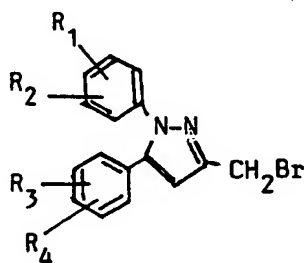
la réaction du dioxobutanoate avec une phénylhydrazine de la formule



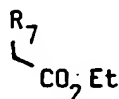
pour former un carboéthoxypyrazole de la formule



la réduction du carboéthoxypyrazole avec un agent réducteur, de préférence de l'hydruire de lithium aluminium, pour former l'hydroxyméthyle analogue correspondant, la réaction de l'hydroxyméthyle analogue avec du tribromure de phosphore, pour former un bromométhylpyrazole de la formule

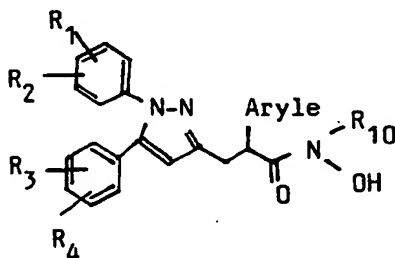


la réaction du bromométhylpyrazole avec un acétate d'aryle substitué de façon appropriée de la formule

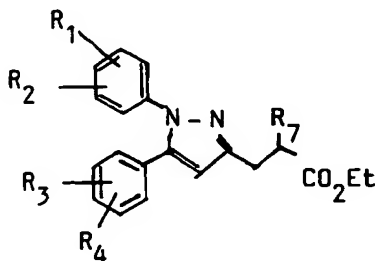


où R_1 , R_2 , R_3 et R_4 sont identiques ou différents et sont choisis parmi hydrogène, alkyle C_1 à C_6 , alcoxy C_1 à C_6 , amino, acétamido, phényle, halo, hydroxy, alkyle C_1 à C_6 sulfonyl, alkylthio C_1 à C_6 , nitro, trifluorométhyle, ω -trifluorométhyle, alcoxy C_1 à C_6 , ou bien où R_1 , R_2 ou R_3 , R_4 , pris ensemble avec le groupe phényle, sont naphthyle ou naphthyle substitué; et R_7 est aryle.

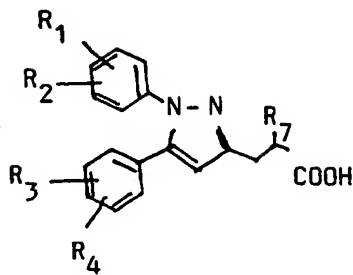
8. Procédé pour la préparation d'un composé de la revendication 1 de la formule



qui comprend la réaction d'un composé de la formule



avec une base, de préférence de l'hydrate de soude, pour former un acide pyrazole propionique de la formule

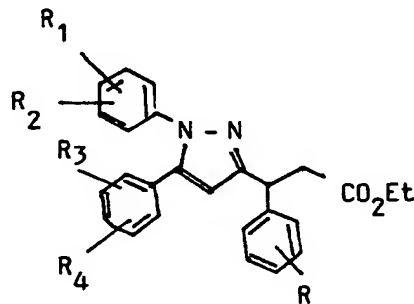


la réaction de l'acide avec du chlorure d'oxalyle pour former le chlorure d'acyle correspondant et la réaction du chlorure d'acyle avec une N-alkylhydroxylamine de la formule

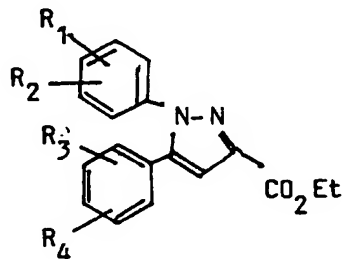


où R_1 , R_2 , R_3 et R_4 sont identiques ou différents et sont choisis parmi hydrogène alkyle C_1 à C_6 , alcoxy C_1 à C_6 , amino, acétamido, phényle, halo, hydroxy, alkyle C_1 à C_6 sulfonyl, alkylthio C_1 à C_6 , nitro, trifluorométhyle, ω -trifluorométhyle alcoxy C_1 à C_6 , ou bien où R_1 , R_2 ou bien R_3 , R_4 , pris avec le groupe phényle, sont naphthyle ou naphthyle substitué; et R_7 est aryle et R_{10} est alkyle C_1 à C_6 .

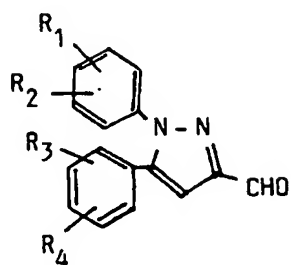
9. Procédé pour la préparation d'un composé de la revendication 1 de la formule



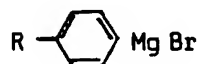
qui comprend la réaction d'un composé de la formule



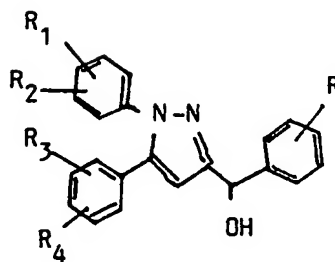
la réduction du carboéthoxypyrazole avec un agent réducteur, de préférence de l'hydrogène en présence d'un catalyseur, pour former l'hydroxyméthyle analogue correspondant et la réaction de l'hydroxyméthyle analogue avec un agent oxydant, de préférence du trioxyde de chrome, pour former un aldéhyde de la formule



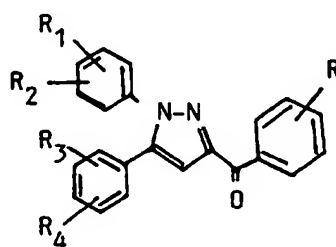
le traitement de l'aldéhyde avec un réactif de Grignard de la formule



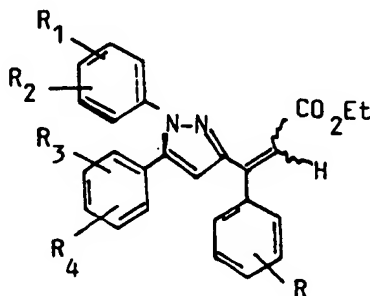
pour former un alcool de la formule



la réaction de l'alcool avec un second agent oxydant, de préférence du chlorochromate de pyridinium, pour former une cétone de la formule

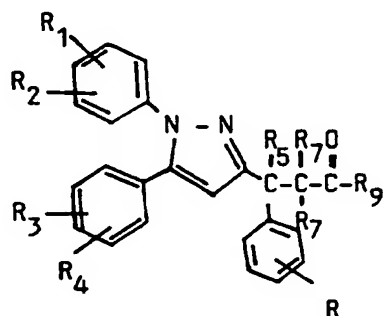


la réaction de l'acétone avec du triéthyl phosphonoacétate pour former un cinnamate de pyrazole de la formule

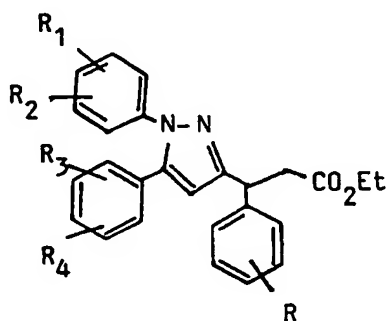


et la réaction du cinnamate avec un agent réducteur, de préférence de l'hydrogène en présence d'un catalyseur, où R_1 , R_2 , R_3 et R_4 sont identiques ou différents et sont choisis parmi hydrogène, alkyle C_1 à C_6 , alcoxy C_1 à C_6 , amino, acétamido, phényle, halo, hydroxy, alkyle C_1 à C_6 sulfonyl, alkylthio C_1 à C_6 , nitro, trifluorométhyle, ω -trifluorométhyl alcoxy C_1 à C_6 , ou bien où R_1 , R_2 ou bien R_3 , R_4 , pris ensemble avec le groupe phényle, forment un groupe naphyle ou naphyle substitué; et R est halo, alkyle C_1 à C_6 , alcoxy C_1 à C_6 ou phényle.

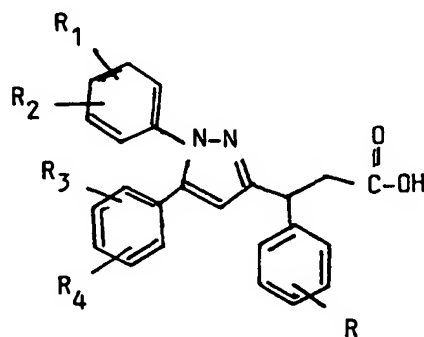
10. Procédé pour la préparation d'un composé selon la revendication 1 de la formule



où R_1 , R_2 , R_3 et R_4 sont tels que définis dans la revendication 1, R_5 , R_6 et R_7 sont hydrogène, R_9 est OH, OR_{10} ou $N(OH)R_{10}$ et R est halo, alkyle C_1 à C_6 ou alcoxy C_1 à C_6 , qui comprend la réaction d'un carboéthoxy pyrazole de la formule



(1) avec un agent hydrolysant, de préférence de l'hydrate de soude, pour former un acide pyrazole propionique de la formule



la réaction de l'acide pyrazole propionique avec du chlorure d'oxalyle et la réaction du chlorure d'acyle qui se forme avec une N-alkylhydroxylamine de la formule

$R_{10}NHOH$

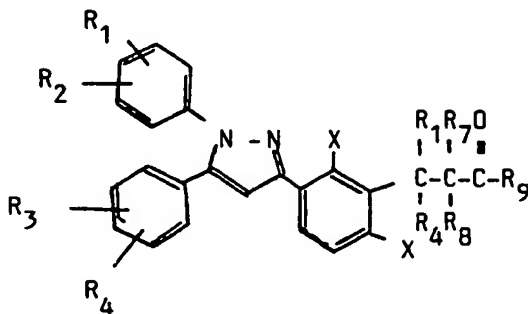
où R_{10} est alkyle C_1 à C_6 .

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11. Procédé pour la préparation d'un composé de la formule

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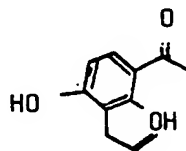
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où R_1 - R_9 et X sont tels que définis à la revendication 2, qui comprend la réaction d'une dihydroxy acétophénone de la formule

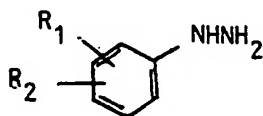
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avec un agent d'alkylation pour former le 2,4-dialcoxy analogue correspondant, la réaction du dialcoxy analogue avec une phénylhydrazine de la formule

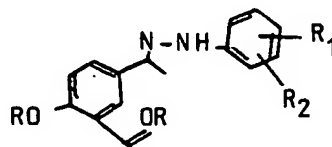
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pour former une hydrazone de la formule

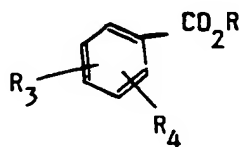
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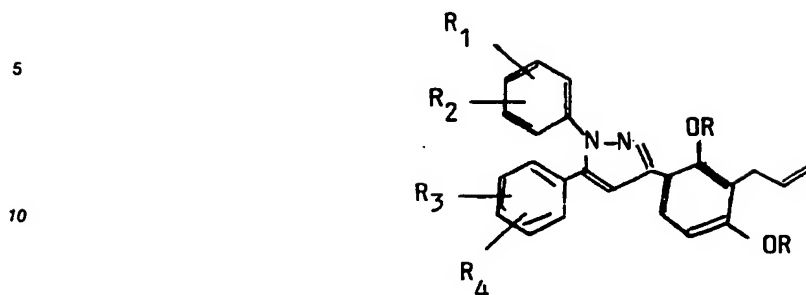
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la réaction de l'hydrazone avec une base, puis avec un ester de benzoate de la formule

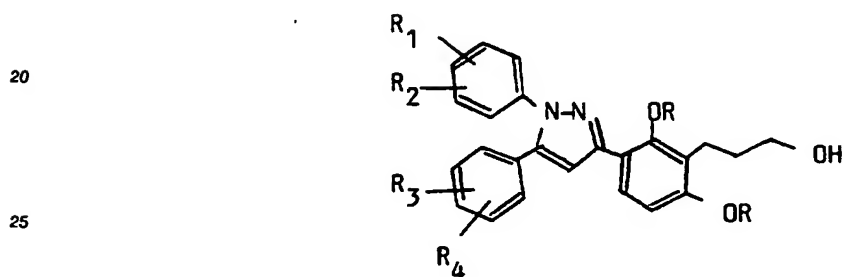
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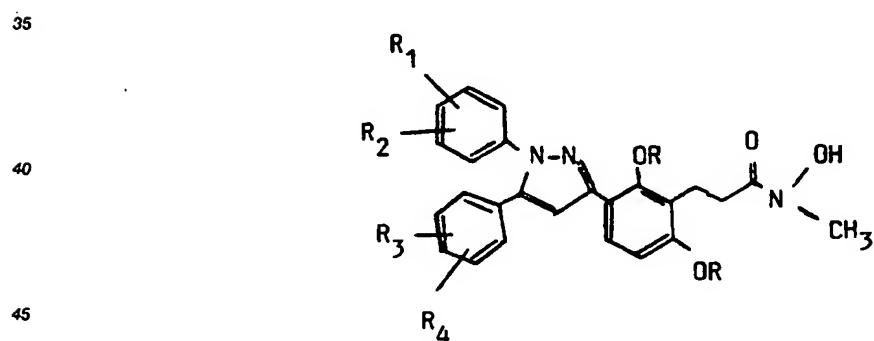
pour former un pyrazole de la formule



15 la réaction du pyrazole avec un complexe de borane-sulfure de méthyle pour former un alcool de la formule



30 et si R₉ est OH, l'oxydation de l'alcool de pyrazole avec un agent oxydant pour former l'acide pyrazole propionique correspondant;
 et lorsque R₉ est OR₁₀, la réaction de l'acide pyrazole propionique avec un agent estérifiant;
 et lorsque R₉ est N(OH)alkyle C₁ à C₆, la réaction de l'acide pyrazole propionique avec un chlorure d'acide avec ensuite la réaction avec une N-alkylhydrolamine pour former un composé de la formule.

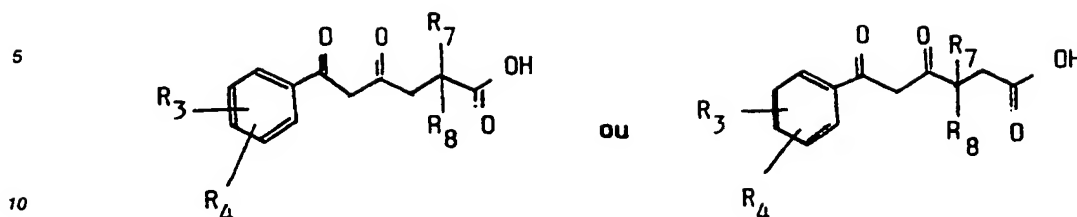


où R est alkyle C₁ à C₆.

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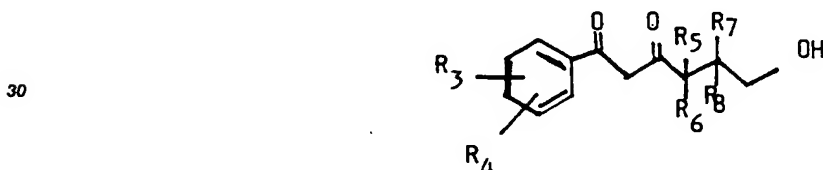
12. Composé de la formule



15 où R_3 et R_4 sont tels que définis à la revendication 1 et R_7 et R_8 sont hydrogène, cycloalkyle, ou alkyle C_1 à C_6 et leurs sels de métaux alcalins, à condition que quand R_7 et R_8 sont tous deux hydrogène, R_3 et R_4 ne soient pas ensemble hydrogène, ni 4-méthyle, ni 3-méthyle, ni 3,4-diméthyle, ni 2-méthyle, ni 4-éthyle, ni 4-chloro, ni 4-fluoro, ni 3,4-dichloro.

20 13. Composé de la revendication 12, choisi parmi l'acide 6-(4-chlorophényl)-4,6-dioxo-2-spirocyclopentyl hexanoïque; l'acide 6-(4-chlorophényl)-4,6-dioxo-3-spirocyclopentyl hexanoïque; l'acide 6-(4-chlorophényl)-4,6-dioxo-2-spirocyclohexyl hexanoïque; l'acide 6-(4-chlorophényl)-4,6-dioxo-3-spirocyclohexyl hexanoïque; l'acide 6-(4-chlorophényl)-4,6-dioxo-2-spirocycloheptyl hexanoïque; l'acide 6-(4-chlorophényl)-4,6-dioxo-3-spirocycloheptyl hexanoïque; et l'acide 6-(4-chlorophényl)-2,2-diméthyl-4,6-dioxohexanoïque.

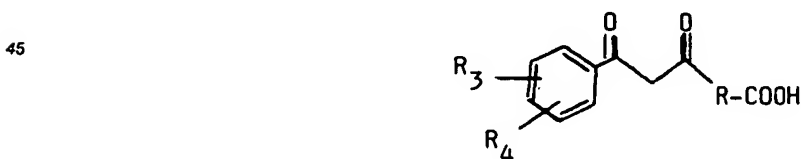
25 14. Composé de la formule



35 où R_3 et R_4 sont tels que définis à la revendication 1 et où au moins l'un de R_5 , R_6 , R_7 et R_8 est alkyle C_1 à C_6 .

40 15. Composé de la revendication 14, qui est choisi parmi le 1-(4-chlorophényl)-4-méthyl-6-hydroxyhexane-1,3-dionate de sodium et la 1-(4-chlorophényl)-4-méthyl-6-hydroxyhexane-1,3-dione.

45 16. Composé de la formule

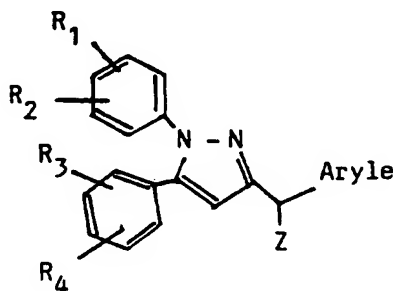


55 où R_3 et R_4 sont tels que définis à la revendication 1 et R est phényle, phényle substitué, pyridyle, pyridyle substitué, cyclohexyle, cyclohexényle ou 7-oxobicyclo[2.2.1] heptényle, mais ne comprenant pas 4'-méthoxy-2-carboxy dibenzoylméthane, 2-carboxy dibenzoylméthane, 3',4'-dichloro-2-carboxy dibenzoylméthane ou des composés où R est phényle, R_3 est hydrogène ou 3'-hydroxy et R_4 est 4'-hydroxy ou 4'-alcoxy.

17. Composé de la revendication 7, qui est choisi parmi 1-(4-chlorophényl)-3-(2-carboxyphényl)propane-1,3-dione; acide cis-1-[1-(4-chlorophényl)-1,3-dioxoprop-3-yl] cyclohexane-2-carboxylique; acide trans-

1-[1-(4-chlorophényl)-1,3-dioxoprop-3-yl]cyclohexane-2-carboxylique; acide cis-[1-(4-chlorophényl)-1,3-dioxoprop-3-yl]cyclohex-4-ène-2-carboxylique; 1-[3-(4-chlorophényl)-1,3-dioxopropyl]-2-carboxycyclohex-1-ène; cis-1-[1-(4-chlorophényl)-1,3-dioxoprop-3-yl]-6-carboxy-2,5-endoxo-3,4-cyclohexène; et 1-(4-chlorophényl)-3-(6-carboxypyrid-2-yl)propan-1,3-dione.

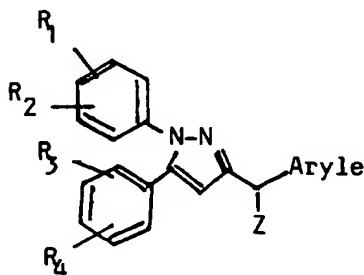
18. Composé de la formule



où Z est choisi parmi OH, =O, =CHCO₂H, =CHCO₂R et =CHCON(OH)R, où R est alkyle C₁ à C₆; R₁, R₂, R₃ et R₄ sont identiques ou différents et sont choisis parmi hydrogène, alkyle C₁ à C₆, alcoxy C₁ à C₆, amino, acétamido, phényle, halo, hydroxy, alkyle C₁ à C₆ sulfonyle, alkylthio C₁ à C₆, nitro, trifluorométhyle, ω-trifluorométhyle, alcoxy C₁ à C₆ ou bien R₁, R₂ ou R₃, R₄, pris ensemble avec le groupe phényle auquel ils sont attachés, forment un groupe naphthyle ou naphthyle substitué; et aryle est choisi parmi phényle, halphényle, mono- ou di-alcoxy phényle C₁ à C₆, biphényle, naphthyle, alcoxy naphthyle C₁ à C₆, tolyle, thiényle et furyle.

19. Composé de la revendication 18, choisi parmi 1-(4-méthoxyphényl)-3-(4-méthylbenzoyl)-5-(4-méthylphényl)-pyrazole, (Z)-éthyl 3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]-3-(4-méthylphényl)-propénoate, acide (E)-3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]-3-phényl-2-propénoïque, acide (E)-3-(4-chlorophényl)-3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]propénoïque, acide (Z)-3-(4-chlorophényl)-3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]propénoïque, (E)-3-(4-fluorophényl)-N-hydroxy-3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]-N-méthylpropénamide, (E)-éthyl-3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]-3-phényl-2-propénoate, (Z)-éthyl-3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]-3-phényl-2-propénoate, (E)-éthyl-3-(4-fluorophényl)-3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]-2-propénoate et (Z)-éthyl-3-(4-fluorophényl)-3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]-3-phényl-2-propénoate.

20. Procédé pour la préparation d'un composé de la revendication 18 ou de la revendication 19 de la formule

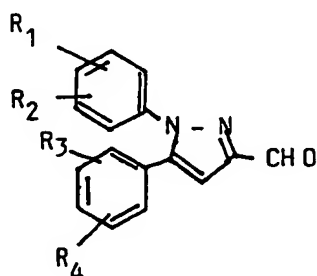


où Z est choisi parmi OH, =O, =CHCO₂H, =CHCO₂R et =CHCON(OH)R, où R est alkyle C₁ à C₆; R₁, R₂, R₃ et R₄ sont identiques ou différents et sont choisis parmi hydrogène, alkyle C₁ à C₆, alcoxy C₁ à C₆, amino, acétamido, phényle, halo, hydroxy, alkyle C₁ à C₆ sulfonyle, alkylthio C₁ à C₆, nitro, trifluorométhyle, ω-trifluorométhyle, alcoxy C₁ à C₆, ou bien R₁, R₂ ou R₃, R₄, pris ensemble avec le groupe phényle auquel ils sont attachés, forment un groupe naphthyle ou naphthyle substitué; et aryle est

choisi parmi phényle, halophényle, mono- ou di- alcoxy phényle, biphenyle, naphtyle, alcoxy naphtyle C₁ à C₆, tolyle, thiényle, et furyle, qui comprend la réaction d'un composé de la formule

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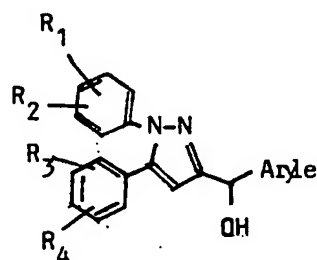


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avec a) un halogénure d'aryl magnésium; ou b) un halogénure d'aryle; ou c) un dérivé arylé activé, pour former un alcool de la formule

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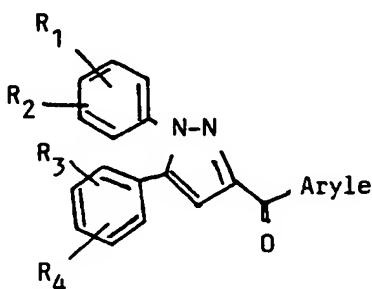


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la réaction de l'alcool avec un agent oxydant pour former une cétone de la formule

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la réaction de la cétone avec un composé de la formule
(RO)₂POCH₂CO₂R

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pour former un ester de la formule

